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Quasi-medical Use of Opium in India and Its Effects

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Contents

		Page
Chapter I.	Historical and general	1
Chapter II.	Policy of the British Government of India with regard to the use of opium	3
Chapter III.	Use of opium in the indigenous systems of medicine and as a household remedy	4
Chapter IV.	Habitual use of opium by adults	7
Chapter V.	Administration of opium to infants	10
Chapter VI.	Quasi-medical use of *post* (unlanced capsules of *Papaver somniferum*)	12
Chapter VII.	Smoking of opium in India	14
Chapter VIII.	Opium consumption in India for quasi-medical purposes—present situation	17
Chapter IX.	Physical, mental, moral and social effects of the opium habit	18

Chapter I

Historical and general

Papaver somniferum var. glabrum, from which opium is obtained, can be grown in any part of India. It is generally cultivated and does not occur in a wild state. Probably the plant is not indigenous to the country but was imported. It is clear from historical records that its introduction dates long before the advent of the British influence into India in the 17th century. The earliest mention of opium, as a product of India, was made by the traveller Barbosa in his description of the Malabar Coast in 1511, and the Portuguese historian, Pyres, in a letter to King Manuel of Portugal in 1516, spoke of opium of Egypt and Bengal.

An excellent account of the history of the cultivation of the poppy and of opium eating and smoking is given by Watt in his " Dictionary of Economic Products in India ".*

History of Cultivation of the Poppy in India

The first recorded instance of the cultivation of the poppy in India, in the 15th century, mentions Cambay and Malwa as the places where it was grown. It appears to have been cultivated first along sea-coast areas and to have penetrated later into the interior of the peninsula. So extensively was the poppy grown in the time of the Mohguls that opium became an important article of trade with China and other Eastern countries. During the reign of the Emperor Akbar in the latter part of the 16th century opium was made a State monopoly. The poppy was mainly grown in Agra and Oudh, and Allahabad, which comprised rather more than the area now included in the present state of Uttar Pradesh; it was also grown in Bengal and Orissa. After the fall of the Mohgul Empire, the State lost its hold on the monopoly and control over the production and sale of opium was appropriated by a ring of merchants in Patna. In 1757, the monopoly of the cultivation of the poppy passed into the hands of the East India Company, who had by that time assumed the responsibility for the collection of revenues in Bengal and Bihar. When Warren Hastings was appointed Governor-General, he brought the whole of the opium trade under the control of the Government. Since then, though changes have been made in the methods of control, of production, distribution, sale and possession of opium, the monopoly has been solely in the hands of the Government and a strict control has been exercised in the best interest of the people of the country as a whole. Under the East India Company and afterwards under the British rule, general cultivation of the poppy and the production of opium were prohibited; these being restricted to three centres :

(1) Patna or Bengal opium, from poppy grown in Bihar and Bengal;

(2) Benaras opium from the United Provinces;

(3) Malwa opium produced in a large number of States of Rajputana, including Gwalior, Bhopal, Baroda, etc. During recent years, cultivation of the poppy has been almost entirely limited to certain areas in Uttar Pradesh State.

Views on Consumption of Opium in India

In 1813 the first Bengal Regulation regarding opium consumption in India was passed and the Government enunciated their policy of restricting the habit of opium-eating by obtaining the " maximum revenue from the minimum consumption ", and declared that they were desirous of countenancing only to the narrowest extent possible a habit which they found themselves unable to eradicate.

Royal Commission. As a result of the activities of the British Society for the Suppression of the Opium Trade, a Royal Commission was appointed in 1893 to enquire into all the circumstances connected with the production and the sale of Indian opium and the Society recorded the opinion that the appointment of the Commission constituted the greatest and most solid forward step that the movement for the suppression of the opium trade had yet made, and considered that the Commission was " as fair-minded and impartial a tribunal as the Society could have desired to hear its case ".

The Commission examined over 700 witnesses from all sections of the population, including 161 medical men. It

* See also : " The cultivation of the opium poppy in India ", by S. N. Asthana, *Bulletin on Narcotics*, Vol. VI, No. 3-4.

examined the various uses of opium, medical and non-medical —namely, the eating of opium, its administration for the doping of children, smoking and use of preparations of decoction from the poppy capsules. It arrived at the conclusion that the smoking of opium and the use of the decoction were rare. The main uses were oral consumption of opium by adults, and administration to children.

The Royal Commission concluded from the evidence collected that the administration of opium to children in the Malwa States was an ancient habit. Abul-fazl, in his *Ain-i-Akbari*, recorded that the use of opium for infants was common in Malwa in the 16th century. Mothers in all ranks of life, while nursing their children, were in the habit of giving them minute doses of opium up to the age of two and a-half or three years. To account for this practice, various reasons were advanced, the principal being the prevention of diarrhœa and other infantile ailments. It was also supposed to correct certain undesirable properties in the milk. Perhaps the chief reason for its widespread use, however, was that by this means the child was lulled to sleep and the mother thus left at liberty to pursue undisturbed her duties in the home or in the fields. A few of the witnesses, chiefly missionaries, who appeared before the Commission were of the opinion that this practice was in part responsible for the high infant mortality then prevalent. The Commission, however, concluded that the age-long practice in the use of opium had resulted in the acquisition of a degree of skill in administering the drug, which must materially minimize the risk of accident, so that evident injury or accidental poisoning, though not unknown, were comparatively rare. The Commission's opinion was that it was impossible to believe that this custom should have been handed down for many centuries amongst a people whose general fondness for their children was well known if it were as injurious as some people seemed to think.

The Commission, on the basis of evidence collected, found it proved beyond reasonable doubt that the prevalence of the use of opium by adults was based first on the universal tendency amongst mankind to take some form of stimulant with which to comfort or distract themselves and, secondly, on the widespread popular belief in the medical or quasi-medical efficacy of the drug. In every part of India, the Commission found witness after witness testifying to the belief in opium as the common domestic medicine of the people.

It was taken in disorders such as rheumatism, diabetes, chill and diarrhœa. As a general stimulant, opium was used in cases of failing strength after the age of 35 or 40. Medical practitioners examined by the Commission were unanimous in their view that the drug was generally used in moderation with beneficial results as a stimulant by those past the middle age. A considerable number of witnesses were of the opinion, from personal experience, that they had derived benefit from the habit. Their experience and vigour were enough to satisfy the Commission that they had suffered no perceptible harm from it, and this was even true of many who admitted that they were in the habit of taking what were considered to be excessive daily doses.

The Commission found strong evidence in favour of moderation on the part of the consumer, and of his general immunity from any evident ill effects caused by the habit. Many of the higher officials of the Government stated that the effects of habitual indulgence in opium by their subordinates had never come to their notice as a reason for dismissal or degradation, though the effects of alcohol had often forced themselves on their attention in this respect. Similar evidence was given by medical officers of experience, both regarding their own subordinates and the men examined by them on behalf of a large railway company and of emigration agencies in Calcutta. The Commission also quoted the evidence of the actuary of the largest insurance company in India in those days that, after twenty years' experience, the company had decided that it was not necessary to impose any extra premium on the lives of moderate opium eaters. They concluded that the use of opium among the people of India in the British Provinces was, as a rule, a moderate use, and that excess was an exception and was condemned by public opinion. The number of people taking opium was, in the opinion of the Commission, a very small percentage of the entire population, and no extensive physical and moral degradation had been caused by the habit.

Ceremonial and social uses of opium. The Commission also referred to the ceremonial and social uses of opium. Amongst the Rajputs, it was considered obligatory as a matter of ancient custom to consume opium on certain religious festivals, such as Holi, Dussehra and the Aksha Tij, at betrothals, marriages, the birth of sons, periods of mourning, etc. The Commission expressed the conviction that it would be impracticable to limit the consumption of opium in India to strictly medical purposes, and expressed the strong opinion that such a measure would be even more clearly impracticable in the case of the Protected Princely States. It could only be enforced, as far as any real enforcement might be possible, by the employment of an army of spies and informers and by a constant intrusion into the domestic concerns of the people. They had convincing evidence to support the view that the habit was not opposed to popular sentiment at that time and that any attempt to suppress it would be in complete opposition to the wishes of the people. They thought it highly improbable that prohibition, if imposed, could be effectually enforced, even if extensive establishments were maintained by the Government of India for inspection and for detection of breaches of the law.

The Commission came to the conclusion that no distinct line could be drawn between the medical uses of opium and those which could not properly be called medical. They pointed out that the chief obstacle to the enforcement of prohibition was to be found in the disposition of the people of India, a matter on which they had specially been required to report by the Order of Reference. From the evidence taken by the Commission, they were convinced that the great mass of public opinion was entirely opposed to prohibition, as an unnecessary restriction on individual liberty and an interference with established native habits and customs. They believed that even those who were not addicted to opium, and who did not belong to the race which commonly use opium as stimulant, regarded the proposal with dislike and suspicion. The use of alcohol was admitted by all Mohammedans, and with few exceptions by all Hindus, to be directly prohibited by their religion. On the other hand, the use of opium was generally considered to be permissible by Hindus, and by all but a few Mohammedans in India. Many able and leading members of the Indian community, Hindu and Mohammedan, not themselves addicted to the opium habit, expressed in their evidence an apprehension that prohibition of the non-medical use of opium would result in an extension of the consumption of alcohol.

Chapter II

Policy of the British Government of India with regard to the use of opium

The views of the British Government of India on the opium policy followed practically up till 1947 are contained in the famous despatch of Lord Harding's Government in 1911, which had become as it were a *locus classicus* of the Government of India on the subject. It reads as follows : " The prohibition of opium-eating in India, we regard as impossible, and any attempt at it is fraught with the most serious consequences to the people and the Government. We take our stand unhesitatingly on the conclusions of the Royal Commission which reported in 1895, viz., that the opium habit as a vice scarcely exists in India, that opium is extensively used for non-medical and quasi-medical purposes, in some cases with benefits, and for the most part, without injurious consequences, that the non-medical uses are so interwoven with the medical uses that it would not be practicable to draw a distinction between them in the distribution and sale of the drug, and that it is not necessary that the growth of the poppy, and the manufacture and sale of opium in British India, should be prohibited except for medical purposes. Whatever may be the case in other countries, centuries of inherited experience have taught the people of India discretion in the use of the drug, and its misuse is a negligible feature in Indian life. Even if it were possible to suppress the cultivation of opium in India, geographical and political considerations would place it beyond our power to prevent illicit import and consumption on a serious scale."

Such was the consensus of opinion at the beginning of the 20th century. Soon, however, the public began to appreciate the harmful effects of the use of this drug, and the policy of the Government began to be criticized.

Public opinion in India against the use of opium. Public opinion in India began to evince great interest in the question of the use of opium. A series of articles were published in the *Servant of India*. An unofficial enquiry was conducted in 1924 by the National Christian Council in India, Burma and Ceylon and its results were compiled by the Reverend W. Paton. His conclusions were exhaustively examined by the Government of India, who decided that they contained nothing that would justify a radical modification of their policy, or that weakened the main conclusions of the Royal Commission on Opium.

Other unofficial investigations were made on behalf of the Indian National Congress with special reference to Assam, where opium was widely used by the people. The All-India Congress Committee in 1924 also passed a resolution stating that the opium policy of the Government of India was contrary to the moral welfare of the people of India, and expressed the opinion that the people of India would welcome the total abolition of the opium tariff for purposes of revenue and that the production of opium was out of all proportion to the medical requirements of India. Among the many petitions presented to the International Opium Conference of 1925 in favour of the world-wide restriction of the traffic in narcotic drugs to the needs of medicine and science was one from India signed, among others, by Mahatma Gandhi and Rabindra Nath Tagore.

In his book *Narcotics in India and South Asia* published in 1930, H. C. Alexander has described how, through the efforts of Mahatma Gandhi and Congress leaders in 1921 and subsequently, the most remarkable reform was achieved in Assam. Referring to the national leader's demand for immediate prohibition, Alexander says : " The official already quoted and some other Europeans I met declare that this would mean the death of thousands of addicts. This seems incredible. I spoke to a prison medical officer, who told me that many opium addicts go to prison, and he never allows them any opium there; in many years' experience, he had only once thought it wise to give a dose for two or three days. For the first few days, he said, the addicts feel very miserable and think that they will die; they continue in a bad state for about a month; after three months without opium, they are entirely new men; robust and strong, hardly recognizable even by their own wives. Testimony to the same effect was given before the Jubbulpore Opium Enquiry Committee; only 5% of the opium addicts who go to prison require the drug, and even they are broken of the habit within a fortnight. Col. R. N. Chopra's account of ' withdrawal symptoms ' is almost to the same effect. The essential thing is that a man should know that his source of supply is cut off. Then he will soon get rid of the craving."

It was concluded that " the commonest cause of opium taking was the association with and example of other addicts ". Disease came next as a cause. Alexander felt convinced that " in parts of the East, especially in areas, whether large or small, in which there is heavy consumption of opium, a strong anti-opium sentiment exists, based on knowledge of the evil effects of the drug and based, too, on a type of puritanism that is wholly indigenous, and which seems to me to rest on a much more profound philosophy of life than the puritanism that survives in the West ".

In 1925, a resolution was introduced in the Council of State recommending to the Governor-General in Council that " early steps should be taken to see that as far as possible only the medicinal use of opium should be countenanced in India ". The Government expressed the view that " any country importing Indian opium can at any moment say that it requires more Indian opium, and the Government of India will not be influenced in the least by any financial considerations. Prohibition can be justified if there are no uses of an article which are defensible; it can be justified if there exists a social evil of such dimensions and of such a character that it cannot be remedied ", and suggested that the policy of the Government should be not prohibition but temperance. The danger of smuggling, the difficulty of putting down illicit cultivation, the difficulty of the Princely States, and the danger that people might be driven to the use of other types of drugs far more deleterious were real. " The danger of over-legislation against opium is that difficulties may be placed in the way of people obtaining it when required medicinally without the prescription or orders of a recognized medical practitioner." The resolution was not passed by the Council of State.

Thus it appears that, whereas various public bodies at various times agitated for the prohibition of opium consumption, the British Government of India, backed by the medical and expert advice at its disposal at that time, held the view that, though they were prepared to take all effective steps to minimize the consumption of opium, they did not find it possible to prohibit its use altogether.

International criticism of the British Indian Government's policy. Use of opium in India evoked much criticism at this time in international circles, especially from America. The policy of

the Government of India in this respect was attacked not only on moral and health grounds, but also on the score of the illicit traffic which was alleged to have originated from India.

The question as to what should be considered " legitimate use " of opium was thoroughly discussed at the Conference leading up to The Hague Convention of 1912, but the Convention did not define such use, and merely provided for effective State control on the production and distribution of opium. The American delegates to the Opium Advisory Committee in 1923 tried to circumscribe the scope of the expression " legitimate use " as intended to include only the requirements for medical and scientific purposes, but from the very beginning, the Indian delegates took the stand that the use of raw opium according to the established practice in India, and its production for such use, were not unlawful under the Convention. In explaining the attitude of the U.S.A. Government towards the Indian reservation, the U.S.A. representative said that he did not desire to discuss questions of purely domestic legislation in connexion with the use of opium, but that the U.S.A. Government did not consider any international traffic in opium for other than medical and scientific purposes to be legitimate except under the conditions explicitly laid down in The Hague Convention.

At the Second Geneva Conference again, the American and some other delegates desired to prohibit the production of raw opium except for strictly medical and scientific purposes by redrafting Article I of The Hague Convention. By limitation to strictly medical purposes, the American delegation intended, as they explained later, limitation to the prescription of medical practitioners holding European or equivalent qualifications. Such medical practitioners were few in number in India and the American proposal would therefore have caused great hardship by *inter alia* precluding all possibility of recognizing practitioners of the indigenous system of medicine. India, therefore, could not agree to the proposal even as a guiding principle. There was a wide divergence of opinion among the delegates on the American proposal, and the text as ultimately adopted had no reference to the restriction of production to medical and scientific needs only. America, however, continued to press its viewpoint.

In 1944, the U.S.A. Government suggested that the British Government should give immediate consideration to the advisability of taking steps, with a view to an announcement at the earliest possible moment, that the use of opium for other than strictly medical and scientific purposes should be stopped. In consultation with the Government of India, His Majesty's Government replied that every effort would continue to be made in future, as in the past, strictly to control the production of opium in accordance with treaty obligations, and explained the circumstances under which opium-eating was tolerated in India. It was also emphasized that it would not be practicable, wise, or indeed humane, to limit the consumption of opium to medical and scientific purposes. The post-war plans for increased provision and wider distribution of medical facilities throughout India would take considerable time to materialize, and the question of finding a suitable substitute, if indeed one could be found and made available, presented considerable difficulty. In the circumstances, the Government of India were of the opinion that a drastic change in the internal policy of toleration of the moderate use of opium under proper Government control was not possible.

Taking note of the general feeling both in India and abroad, the Government of India, however, started to take positive steps towards reduction of production and consumption of opium in the country.

Prohibition of opium-smoking. In November 1946, the Government of India, in consultation with Provincial Governments and Indian States, decided to prohibit altogether the smoking of opium in British India, exception being made only in the case of existing addicts so long as they survived, and subject to their producing medical certificates in terms prescribed. An announcement in the form of a Government resolution in these terms was made on 20 November 1946. The provincial Governments were asked to take steps to implement the decision announced by the Government of India wherever necessary and action in this behalf was taken by them either by legislation or by amending their rules. The Indian States generally followed these lines.

Prohibition of opium-eating. Later, in deference to international opinion, the Government of India accepted and declared as their policy " the prohibition of opium production except for medical and scientific use " and that they would " endeavour to give effect to this policy at the earliest possible date compatible with effectiveness ". An announcement in these terms was made by India's delegate to the fourth session of the Economic and Social Council, held in New York in March 1947. Similar views were expressed by India's delegate to the second session of the United Nations Narcotics Commission in July–August 1947, when it was stated that the " policy of the Government of India on exports had been under revision, and its present policy was definitely to discourage cultivation except for medical use. The Indian Government was not interested in exporting opium for profit, and very little profit was actually made by the Central Government."

In the session of the Indian Parliament held in March 1948, this statement was reiterated. It was also announced that in respect of centrally administered areas the policy of prohibition had been accepted.

Progressive annual 10% cut in production and internal supplies. In August 1948, the Government of India requested the Governments of Provinces, States and State Unions to make a progressive reduction of 10 per cent per annum in their indents for the supply of excise opium, and the authorities at Ghazipur and Neemuch factories issuing the opium were similarly directed to cut down indents by 10% where such a cut had not already been effected (as compared to the previous year's supply) by the indenting Government. A corresponding progressive cut of 10% is being made in the area under poppy cultivation in Uttar Pradesh and the producing States and the State Unions have been requested to follow suit.

Chapter III

USE OF OPIUM IN THE INDIGENOUS SYSTEMS OF MEDICINE AND AS A HOUSEHOLD REMEDY

From the very earliest times opium has been used in medicine. We have already referred to the use of opium by the ancient Greek physicians. Hippocrates, nearly four centuries before the Christian era, recommended the internal use of opium. Pliny gave a description of opium and its medical use; Galen spoke enthusiastically of the virtues of opium and the drug

soon found its way into Roman medicine. The Arabian physicians used opium extensively in their practice and there appears to be little doubt that it was through their agency that it was introduced into Indian medicine.

No exact statistics are available regarding the use of opium in hospitals and dispensaries in India, but, from a general survey made, it would appear that the use of opiates by the practitioners of Western medicine in this country is limited. While addiction to narcotics resulting from physicians' prescriptions is common in Europe and America, in the whole of a series of nearly 900 cases examined by us not a single individual was encountered who could attribute his habit exclusively to such a factor. The reason is that the practitioners in this country are fully aware of the consequences of such addiction and hesitate to prescribe opiates unless it is absolutely necessary and then only with great caution.

Opium in the Indigenous Systems of Medicine

Opium in Ayurvedic or Hindu medicine. No reference has been made in the ancient books on Hindu medicine either to the poppy or its products. The exact time at which opium was introduced into Ayurvedic medicine is difficult to determine. In the classical works of *Charaka*, *Sushruta* and *Veghbatta*, no mention is found of opium. The last of these works is believed to have been written in the 6th century A.D. The author and the commentator, Chakrapani Dutt, who, on his own statement, lived in the reign of King Nayapala of Bengal (11th century), does not mention opium in his work on the practice of medicine commonly known as *Chakradutta*. It is, however, contended that in an old work on toxicology by Narayan of Malabar about 862 A.D., the use of opium in the treatment of "rat-poison" has been mentioned.

In later works such as *Sharangadhar Samhita* and *Bhavaprakash*, opium is freely mentioned in the *materia medica* section and used in several preparations. According to all modern investigators of Ayurvedic chronology, Sharangadhar lived in the 14th century and Bhavamisra in the 16th century. It is probable therefore that opium came to India along with or a little before the Mohammedan conquest. It was fairly extensively used by the Hindu physicians in the 15th century. Later on, especially during the last two centuries, the use of this drug has extended and there are as many as eight preparations containing opium used by the Ayurvedic practitioners :

1. *Karpura rasa*
2. *Ahiphenasava*
3. *Brihat Gangadhar churna*
4. *Makandeya churna*
5. *Dugdha vati*
6. *Grahanikapta rasa* (Rasendra sara sangraha)
7. *Akrakaravadi churna* (Sarangadhara)
8. *Sambhunath rasa* (Bhaishajya tantra)

It may be stated at once that opium is not used to a very great extent in the Ayurvedic medicines at the present time. Its administration is mainly confined to two diseases, namely diarrhœa and dysentery, and it is only given in certain stages of these conditions. It is said to cure the concurrent derangements of the three humours, increase the sexual and muscular powers and produce stupefaction of brain. The curious fact is that Hindu physicians never made much use of the sedative and pain-relieving properties of opium on the human organism and even now it is said to be used only occasionally to relieve pain and spasms.

Opium in the Tibbi or Mohammedan medicine. In the Mohammedan or Tibbi medicine the introduction of opium naturally came from Arabian medicine, from which this system originated. The Arab physicians Razi and Arisina gave a detailed description of opium many centuries ago. It is described as an anæsthetic and its powers of alleviating pain were fully appreciated. The Tibbi physicians prescribe it for headache, hemicrania, pain in the eyes and ears, pain in the teeth, lumbago and pain in the joints. Not only is it given internally by them, but it is also applied externally in the form of paints. The astringent or constipating property of opium was responsible for its use in diarrhœa and dysentery. The Tibbi physicians believe that opium has hæmatinic or blood-regenerating properties. With regard to its action on the brain, they hold that at first it stimulates the brain temporarily and gives rise to sensations of pleasure and satisfaction, increase of physical vigour and a feeling of warmth. They attribute its continuous use leading to habit formation to these properties. The narcotic and sedative properties of opium were fully appreciated by these physicians and it was prescribed in mania, delirium and inflammatory conditions of the brain, both internally and externally. It was also used in catarrhal conditions of the mucous membranes, paralysis agitans, facial paralysis, epilepsy and other nervous conditions. The sedative action of opium on the respiratory tract was also appreciated and it was largely employed to allay severe cough, asthma and hiccough. The Mohammedan physicians also advocated it as an aphrodisiac as it was believed to lengthen the time of seminal discharge during coitus; it was prescribed also in spermatorrhœa. It is also believed to be an antiperiodic and is recommended especially in fevers of intermittent type. At the present time opium is used by the Tibbi physicians mostly in combination with other drugs in the treatment of diabetes mellitus. It will be seen, therefore, that, while the Hindu physicians knew little about opium and its properties, the Mohammedan physicians had a much more extensive knowledge of this drug and used it more extensively to relieve pain and in other conditions.

The following preparations of opium occur in the Tibbi *materia medica :*

1. *Barshasha* — An old compound of opium which is used even now in catarrhal conditions of mucous membranes, cough, delirium, epilepsy, diarrhœa, hæmorrhage, premature seminal emission, etc.
2. *Hub-i-pecheash* or dysentery pill used in dysentery.
3. *Hub-i-jadwar* — A renowned compound of opium used against catarrh, coryza, cough, diarrhœa and premature seminal discharge.
4. *Hub-i-siyah* or black pill. It is made into paste and is painted on the lids in conjunctivitis and ocular pain.
5. *Hub-i-sarfa* or cough pill.
6. *Hub-i-haiza* or cholera pill used in cholera.
7. *Kurs-i-massallas* or triple tablet used against headache and painful conditions. It is made into a paste and used as a paint.
8. *Hud-i-Mumsik* or aphrodisiac pill used against premature seminal discharge.

Investigations by Chopra (1928) show that, although opium became very popular in India and fell into the hands of

shopkeepers and itinerant quacks who made use of it for all sorts of conditions, its use in both the Ayurvedic and Tibbi systems was on the whole comparatively limited. This is borne out by other investigators also. In a memorandum presented to the National Christian Association of India, Burma and Ceylon, the Social Service League of Bombay (1924) said: "Medical practitioners following the Ayurvedic and Unani systems very rarely prescribe opium, and even when they think it necessary to use that drug, they do so in medicines prepared by themselves in most of such cases." On the other hand, it has been frequently said that Kavirajes and Hakims largely prescribe it and are responsible for the freedom with which it is resorted to in sickness by the people.

We have carefully examined this allegation and find that properly trained practitioners of the indigenous systems at the present time do not advise the use of opium to any large extent and, when they do use it, they do not give raw opium, but give it as a constituent of one of their preparations. We have enquired into the preparations commonly used by these systems and find that very few preparations containing opium are extensively employed by these practitioners. Out of 200 to 250 stock preparations of Ayurvedic medicines kept in the main dispensary of the Ayurvedic and Tibbi College of Delhi, we found only three preparations containing opium and, on going into the consumption of these particular preparations, it was found that they were very sparingly used. The same was found to be the case in the Tibbi Dispensary of that institution.

Opium as a household remedy. We have said that the amount of opium used for purely medical purposes in the indigenous system of medicine in India is very small, but it is largely used by itinerant quacks and shopkeepers who, because of its easy accessibility, and because of its well-known property of relieving pain and bowel conditions, advocate its use indiscriminately in a large variety of common ailments. Dr. Roberts, in his minute in the report of the Opium Commission, stressed the use of opium as a household remedy in India, but his conclusions even at that time were severely criticized and challenged. He said that the drug had been used for centuries and that the people were familiar with its internal and external use. The conditions in which it was used by the lay people were cough, bronchitis, asthma, diarrhœa, dysentery, colic, chills, hæmorrhoids or piles, recurrent febrile attacks, neuralgic troubles, malarial fevers and cachexia, rheumatic pains, diabetes, gravel, nervous troubles and indeed all painful and wasting diseases of every kind.

The use of opium as a prophylactic against malaria was also emphasized in his memorandum. The local consumption of opium in many parts was said to bear a close relationship to the prevalence of malaria. The Commission was informed by many witnesses that this extensive semi-medical use of opium was due to the fact that large masses of people were beyond Western medical aid, that the unrivalled power of opium in alleviating pain and producing sleep and of controlling intestinal fluxes which were so much dreaded, made people resort to it. It was said that not more than 1% of the population ever consulted a medical man and a great majority lived outside the reach of expert advice. Most of them consulted Vaids and Hakims who invariably gave them opium in bowel conditions or when there was pain.

These points were thoroughly investigated and, as already stated, it was found that properly trained practitioners of the indigenous systems do not use large quantities of opium in their practice. There was also no evidence in support of the view that opium was used more as a household remedy in those areas in which medical aid on Western lines was not available. Investigations in the Punjab showed that the consumption of opium was related more to the class of the population residing in an area than to facilities of medical aid in that area. In some districts of the Central Punjab, chiefly inhabited by the Sikhs, where a large number of dispensaries and hospitals had been established and ample provision was made for medical relief on Western lines, much more opium was used than in some of the northern districts which were inhabited by Mohammedans, whose religion forbids the use of narcotics. Observations in the field confirmed the fact that much of the household or semi-medical use of opium was due not to scarcity and expensiveness of qualified medical men, but to the prejudice which existed among ignorant people against Western medicine.

It was also not possible to confirm the assertion that opium was used much as a household remedy for its supposed prophylactic or curative effects against malaria. In some of the districts of the Punjab along the course of such rivers as the Jhelum, the Chenab and the Indus, where a virulent type of malaria prevailed and spleen index was very high, the consumption of opium was very small indeed, while in some of the comparatively dry and healthier areas the consumption was enormous. There was no prevalent belief among the rural population regarding the efficacy of opium in preventing recurrence of attacks of malarial fever though it undoubtedly ameliorated the symptoms.

Dr. Roberts suggested that possibly "anarcotin" or narcotin which occurs in opium and which, according to him, resembles quinine, may have anti-malarial properties. This alkaloid was tried in a number of cases of malaria but no clinical or experimental evidence was forthcoming to support the claim that it possessed any significant anti-malarial action. It is true that the people of India in former days had prejudice against quinine and other anti-malarial drugs of Western medicine and preferred to resort to other remedies which might be soothing but not curative. But the prejudice was not deep-rooted and was entirely overcome.

As regards the use of opium in checking debilitating factors such as diarrhœa and preventing chills, it is true that there was and there still is a widespread belief among the people regarding the efficacy of opium in bowel diseases and they use it either on their own initiative or on the advice of itinerant quacks. Sometimes the results are apparently good but occasionally they are disastrous.

The use of opium as a household remedy is ascribed to a belief said to be prevalent among the people that it gives protection against damp and that it wards off the approach of fatigue. These points were constantly brought up before the Opium Commission as arguments against restricting the use of opium to purely medical and scientific purposes. It was contended by competent authorities that to deprive the people of the possession of "such a wonderful household remedy as opium would be a terrible and wanton cruelty, as it was the only medicine of any value that is available to them".

So far as the effects of the drug in keeping off damp and cold are concerned, the investigations of the authors in the Punjab particularly, and in other parts of India generally, show that opium was not much used for this purpose. The thickly populated areas along the course of some of the Punjab rivers are inundated every year for many miles on either side

of their banks and to the extent of four to five months in the year during the hot weather, on account of melting of the snows in mountains and later owing to the rains. Little or no opium was used in those areas although the inhabitants were constantly living in close proximity to water. The same was the case in many districts of East Bengal, where a large proportion of the population lives practically in water for many months in the year.

So far as the use of opium in warding off fatigue is concerned, careful observations have shown that opium undoubtedly dulls the individual's sensitiveness to fatigue by depressing his higher faculties and giving him a feeling of drowsiness, but it has no effect whatsoever in averting fatigue or increasing his capacity to work. On the other hand, it is a well-known physiological fact which needs no corroboration that the capacity of an individual to do mental or physical work is considerably reduced when he is under the influence of narcotic drugs such as opium.

It was obvious, therefore, that it would be no hardship at all to the people of this country if they were to be deprived of the use of opium, as far as its alleged use as protection against damp and for warding off fatigue is concerned.

Use of opium for veterinary purposes. It has been said, and reference has also been made to it in literature, that large quantities of opium are given to animals and that a considerable portion of the opium sold is thus used. It was believed to be given to elephants, horses, cattle, etc., and it was held that very large quantities were used in this way. Whatever might have been the case in the old days, our investigations in the Punjab and Bengal particularly and in other parts of India generally showed that the custom of giving opium to domestic animals was not at all common and is rare at the present time. With the exception of Afghan horse dealers who bring quantities of opium to give to their horses and of thieves and dacoits who administer it to their animals supposedly to enable them to endure heavy physical strain, it was hardly ever used. Its very high price precludes its being used in the large quantities which it would be necessary to administer to domestic animals in order to produce physiologic effects. The use of opium in veterinary practice is also not very extensive.

Chapter IV

Habitual use of opium by adults

The use of opium in India could best be discussed in three phases : first phase, until 1893 : no restriction on the production and sale of opium to the public, low prices ; second phase, 1893-1948 : leading to the present régime of restriction; third phase, present situation (this third phase is dealt with in Chapter VIII).

* * *

First Phase : until 1893

That the use of opium was prevalent in the time of Akbar is shown by references made to it by Abul Fazl in his *Ain-i-Akbari*. He states that even the Emperor occasionally indulged in taking opium and " Kuknar ", a beverage prepared from the poppy capsule. Most of the nobility of the court of Akbar and Jahangir used a beverage, composed of a mixture of hemp, opium, wine and kiknar, called " Charburgha ". It is a well-known fact that large quantities of opium were consumed in Oudh during the reign of the dynasty which ruled there until recently. The testimonies of European travellers confirm that in the 16th century opium indulgence attained considerable magnitude in India. It was mostly eaten, as no mention is made about opium-smoking.

Habitual indulgence in opium by smoking has always been considered a very uncommon practice in India (see Chapter VII). The general practice was to pound the drug and mix it with water. Such a mixture was known as " Kasumba " and was taken in the form of a drink. Mostly, however, it was taken in the form of a pill. The majority of the people who took opium habitually took it once a day, generally in the afternoon, but often it was taken twice a day—i.e., in the morning and in the afternoon. Rarely it was taken three times a day—i.e., morning, afternoon and night. Generally, crude opium purchased from the excise shops was used, but not infrequently it was mixed with such other ingredients as saffron, musk, sugar, etc., and then made into small pills.

That the habit of opium-eating was not confined to the nobility of the court but prevailed extensively among the people generally is clear from historical records. Dr. Hove, a Polish traveller who visited India in 1787 and spent much time in Western India studying the habits of the people, said that a beverage made by dissolving opium in water was commonly used by the people. The habit appears to have prevailed extensively among the population, but no authentic records are available to show the extent to which it existed prior to 1857 when the cultivation of opium was brought under control by the British Indian Government. From the general description given by various writers, it would appear that the opium habit was much more prevalent in this country during the 17th and 18th centuries than in the last quarter of the 19th century.

As long ago as 1735, Warren Hastings laid down the principle that opium was not a necessity of life but a pernicious article of luxury which ought not to be permitted, and " which the Government should carefully restrain from internal consumption ". Investigation by Watt (1881) showed that the consumption of opium had gone down considerably since the advent of British rule in India. There is, however, no doubt that use of opium was extensive and considerable. It has been said that so general was its moderate use that it may be likened to the use of beer, wines and spirits in England. It was said to be largely indulged by people over 40 to 45 years of age and even by people who by conviction were total abstainers from all intoxicants. It was said to sustain life and it did not in any way bring social stigma on those who indulged in it especially after that age. It was believed to stave off aches and pains of joints, to keep down cough, expectoration and diarrhœa, etc., common among the aged people. Its use was therefore not considered unreasonable. In younger people it was taken generally for disease or physical ailments and not generally on medical advice. Persons below 30 years of age indulged in it for its pleasure-giving properties, not infrequently with a view to excite the sexual instincts and prolong the sensual gratification. All classes of society and both sexes were said to indulge in it freely.

The practice of taking opium on ceremonial occasions such as marriages, deaths, etc., and on semi-religious grounds has also been mentioned. This might have been the case in certain small areas in parts of India such as Rajputana and

Gujerat, but the present authors did not come across it anywhere in the areas which were investigated by them.

Some writers have gone so far as to say that it was a necessity of life in tropical countries in that it afforded protection against fevers and the depressing effects produced by them. Gavit (1925), in his book *Opium*, speaking about India says : " Something like half the opium produced in India is consumed in India for pseudo-medical purposes and in the ancient practice of eating and drinking opium and almost universally feeding it to infants, as well as to livestock including elephants."

Be that as it may, there is no doubt that, in spite of its unrestricted availability and its low cost, the total consumption of opium in India at that time was infinitely smaller than in China and other opium-using countries in the East. This can easily be shown by comparing the figures of the excise revenues of various countries concerned. Roberts (1895), after carefully sifting the evidence before the Opium Commission, came to the conclusion that, taking India as a whole, it may be said that only a small minority, even of the adult male population, took opium habitually.

* * *

Second Phase : 1893-1948

The first comprehensive study of the problem began with the appointment of the Royal Commission in 1893 (see Chapter I above), but even the evidence placed before the Commission was of a general nature, dependent on personal experience of individuals and hearsay and, despite the investigations referred to in Chapter II, the medical and scientific aspects of the problem and the effects produced on the health by the habitual use of opium were unknown.

It was only in 1928 that Chopra and his co-workers took up a detailed study of indulgence in opium all over India and effects produced by it. They collected very useful statistics of consumption from the excise records of different parts of the country and from their own work in the field, to gauge the extent of the opium habit in the country during this period. They were forcibly struck by the fact that the habitual use of opium was not nearly so common in India as might have been imagined from some of the publications dealing with this question. Its incidence among various peoples was very irregular and although there were certain areas and certain classes of the population which were badly affected, these formed a very small minority. William Paton (1924), of the National Christian Council, after carefully sifting the evidence obtained by the Council, said : " Taking the country as a whole, it is comparatively rare."

The habitual use of opium was not nearly so common among people during the period when life begins to show signs of decline as it was said to be during the end period of Phase I. The considered opinion was that, although there were many people who took small doses—½ to 3 or 4 grains a day—when they had passed the age of 45 or 50 and when their vitality was on the wane, this was by no means a common practice in most parts of India. If the accounts of the prevalence of the habit given by writers of the last century (during Phase I) are true, there must have been an enormous decrease all around in the use of opium in India. Investigations in the Punjab showed that in the central districts of that Province, populated chiefly by the Sikhs, where the consumption of opium recorded is perhaps the highest with the exceptions of Assam and Calcutta, the percentage of habitual consumers was less than 1% of the total population. In most of the other districts of that Province, the consumption of opium was not above the standard of 12 lbs per 10,000 of population per annum laid down by the League of Nations for strictly medical and scientific purposes. The proportion of people indulging in the habitual use of opium was not much more than 1 in 50,000 in most places.

A detailed study of consumption figures by district throughout India carried out by Chopra (1928) showed that, while there were large tracts in the country where opium consumption was even lower than the League of Nations standard, there were others where it was very high. The Government, however, were taking very great interest in these areas and had appointed local committees to enquire into the causes of the high incidence of addiction there and to make recommendations with a view to their eradication. These committees submitted their reports and suggested such measures as compulsory registration of addicts, further raising of price, stricter regulations regarding retail sale, sale on medical certificate only, etc. These were gradually introduced.

From the study of the statistical and other records and from his own work in the field, Chopra concluded that only a small fraction of the population of this vast country indulged in opium habitually. It was also shown that the habit was on the decrease on the whole, and that it certainly was not spreading. These investigations also showed that during the period 1920 to 1940 addiction had decreased much more rapidly than in the years previous to that period. This is also borne out by the fact that the quantity of excise opium issued for consumption in British India including Burma was reduced to nearly half since 1911/1912.

1911/12 . . .	1,031,227 lbs	
1919/20 . . .	855,721 lbs	
1925/26 . . .	600,784 lbs	
1947/48 . . .	566,456 lbs	(excluding Burma, but including the Princely States).

It was concluded from these observations " that the factors which have been chiefly instrumental in reducing the consumption of opium in India are decrease in its production and increase in its price ".

Causes leading to the use of opium. Under the first group come all those who resort to the drug because they find that it gives them relief from certain diseases or minor ailments from which they suffer. Pain and disease seem synonymous in the conception of many people and as opium relieved pain this had given rise to the popular belief that opium was a panacea. Most of the people were their own physicians, because proper medical aid was not available or was too expensive for the regular and protracted treatment required for some of their ailments. Opium was often taken on the advice of a friend, a relation or a quack to relieve some obstinate complaint. This relief was more often obtained than not and the habit not infrequently was formed and persisted with the result that soon the sufferers became slaves to it.

A considerable portion of the population resorted to very primitive methods of treatment and this was very largely responsible for the use of opium as a household remedy. They made use of opium, failing to realize the fact that it was only a palliative and had no curative action. The word

cure is not clearly defined in their minds; temporary disappearance of a distressing symptom is considered to be a cure, and the dose is repeated again and again. Most of them start with a small dose and stick to it. For many of them the euphoric action of the drug apparently has little or no attraction, the relief of the ailment being the paramount consideration. A comparatively small number of this group, however, fall victim to the euphoric action of the drug and increase the dose in the same way as an addict who has contracted the habit purely for its euphoric action.

In the series of nearly a thousand cases studied, as many as 40 or 50% of the addicts came under this category. The diseases which figured most commonly amongst this group were of a minor character, the commonest being pain of a neuralgic type, joint pain, digestive and respiratory affections, diarrhœa, and cough. In the whole of this series there was no single case of severe or incurable disease for which opium was taken on medical advice.

The habit in all these cases was by no means as innocent as has been described. In a number of these individuals the habit thus formed developed into a vice and the drug was taken as a panacea to alleviate the physical and mental ills which had resulted from the life these people had been living. Even those individuals who started the drug purely for the relief of ailments and pain not infrequently began to feel pleasure and comfort from its anodyne effects, and were likely to continue its use even when their condition was relieved. In fact it may be said that, if the exhilarant and stimulant effects of opium were entirely left out (leaving only the physical and pain-removing effects), 95% of the addicts would not use it. Our experience was that relapse, in cases of most of the addicts who had conscientiously tried to give up the habit, was not due so much to ill-health as to the insatiable desire to experience the pleasurable effects of the drug. There was, however, a very small minority of individuals in whom the habit was acquired purely on account of physical disease and discomfort, there being no psychopathic taint. In them the habit could be easily eradicated if the condition was relieved.

The second group comprising about 20 to 30% (in this series) included the persons for whom the strains and stresses of life had become unbearable and who took the drug to forget their worries and anxieties. Some of these were quite genuine cases and might have come from any strata of society. They were tillers of the soil, daily labourers, people following different professions or vocations in life. Social and economic conditions prevailing in the country often threw a great strain especially on the elder earning members of the family. People often had to work hard to a ripe old age owing to the loss of the younger earning members of the family. A number of these were also inadequate personalities, nervous and over-sensitive in type, highly strung individuals who were unwilling or thought they were unable to stand the physical or mental stress of life and resorted to opium with the idea of warding off fatigue or staving off the effects of old age so as to enable them to carry on their work. They fondly imagined that the drug would increase their physical powers and would enable them to do more work. From their point of view the apparent results were extraordinarily good. There is no doubt that opium, on account of its analgesic effects, does enable a person suffering from pain or a minor ailment to undergo physical exertion which otherwise would be impossible for him, but this only puts extra strain on the system and has a baneful effect on the constitution in the long run.

With regard to the effects of opium in staving off the onset of old age, it was represented to the Opium Commission by many witnesses that the habit was mainly one of middle life and was comparatively rare among young adults. The habit, it was said, began between 30 and 40 years of age, when vitality was on the wane and the premonition of old age came on. This epoch, it was said, occurred much earlier in Indians than in Europeans. The use of small quantities of opium taken during this period of life was stated to have a beneficial effect on the longevity of the individual. This idea undoubtedly was very prevalent at one time, and a large number of people took small doses of opium ranging from 1 to 4 grains per day after they had passed the age of 50 and were convinced of its beneficial effects. Such is no longer the case. While in the series of cases referred to there were some old people who had taken small quantities of opium ever since they had passed the age of 50, it could not be said that opium was responsible for prolonging their life, as similar cases occurred among people who do not eat opium and perhaps with greater frequency.

The third group of addicts or the euphoric type was composed of those persons who took opium for the purpose of self-gratification; these in this series comprised about 15 to 30% of the total addicts. Although their occurrence was noted among the rural population, they were much more commonly met with in the cities because of the overcrowding and the insanitary surroundings which existed there and because of the lack of facilities for open air and healthful recreations. This type of addiction generally occurred between the ages of 20 and 35 and was on the increase both in cities and rural areas during this period while the other types showed a decrease.

As already pointed out, some used opium for its aphrodisiac action as it was a common belief that it increased the pleasure of the sexual act. It is a well-known fact that this drug stimulates the body to endure excesses of all kinds to which it is driven by mental depravity which it itself produces. Others belonging to the leisurely and idle classes started taking the drug for the mere fun of it. They tried the drug through sheer curiosity in periods of idleness and became addicted to it to escape the monotony of their life. Its use amongst this class may be said to be traditional, as ever since the time of the Mohguls it had been considered to be a luxury habit of the rich classes. They were the classes of people who fell an easy prey to the soothing effects of the drug and, appreciating the comfort it afforded them, readily developed the habit.

There was yet another type in which the psychoneurotic factor played an important part. These addicts generally were weak-minded individuals who developed the most vicious type of habit and who rapidly sank very low. In this group were also included a large criminal class who often started taking opium under the impression that it fortified them and enabled them to bear the physical and mental strain connected with their nefarious work. They often increased the dose and the euphoric factor became prominent in many of them. Not infrequently they also used other drugs such as *Cannabis*, alcohol, cocaine, etc. Our investigation in the jails showed that a large percentage of the criminal population in these places was addicted to opium.

Types of Indian Habitués to Opium. From a careful study of the large number of people who used opium habitually, Chopra (1928) concluded that Indian addicts indulging in small doses of opium were in no way different from addicts elsewhere. No person, whether an Indian or belonging to any other nationality, is innately addicted to this drug. It is a well-known fact that the basic factor underlying addiction to opium or to any other narcotic drug is in most cases some abnormality in the mentality of the individual. The causes leading to the use of the drug are the same all over the world. The reason for which the drug is taken is sufficiently convincing to the addict himself and he takes it in spite of its dangers. The reason is not physiologic or pathologic but generally of a psychological nature. The great majority of *habitués* in this country are not of the vicious type at all. They tell you that they take the drug for no other reason than that having once started it they do not feel normal without it. Life to them under the influence of opiates is brighter and their surroundings are more pleasant. Sensitiveness to the " pin-pricks " of life is dulled by it, they cannot feel happy without opium and this leads to the repetition of the dose.

A perusal of what has been said above will show that in the large majority of people who took opium, the use was always started for some disease or ailment or to strengthen the body against invasion of disease.

Chapter V

Administration of opium to infants

Incidence in Different Parts of India

That the custom of giving opium to infants prevailed in India there is no doubt. During the time of the Mohgul Emperor Akbar, prevalence of this practice has been recorded in the passages which occur in Abul Fazl's *Ain-i-Akbari*. Opium was given to infants because of its power of allaying diarrhœa and vomiting and of relieving pains such as colic, which often afflict children. According to Roberts, the administration of opium to infants was considered as part and parcel of the household and popular use of this drug. Its use as a household remedy for children's ills was prevalent in the United Provinces (now Uttar Pradesh), Rajputana and Malabar and other parts of India. William Paton, writing in 1924 about the use of opium in children, says, " in almost every part of India it appears that the custom of giving opium pills to small children prevails ". Usually it was not continued beyond the age of 2 or 3 years, but up to that age it was said that the custom was distressingly widespread. The real reason for which opium was given was to stop the child from crying and to ensure sleep when the mother was away at work. All sorts of virtues both prophylactic and curative, however, were attributed to the drug.

Some believed that opium acted as a stimulant and that the children became fat and robust if small quantities of opium were administered and would not do well without it. Others believed it to be preventive of many diseases, especially those of the respiratory and digestive tracts. It was also said to keep the child warm and to afford protection from cold. It was given to children especially during the teething period to allay diarrhœa, peevishness and salivation. Opium was also said to be given to appease hunger among the poverty-stricken masses and to keep the baby warm in cold weather on account of its heat-generating properties.

As far as Northern India is concerned, investigation by Chopra and co-workers (1934) showed that the custom was practically non-existent 40 years ago. In the Simla Hills it was found that opium was fairly extensively given to children, for the women have to work all day long in the fields and their customs forbid them taking children out of their homes until they are 2 years old. Besides, poppy was grown in those parts and raw opium was easily obtainable. In the Punjab, particularly in the Central districts, which are populated chiefly by the Sikhs and where the consumption of opium recorded was one of the highest in the whole of India with the exception of, perhaps, Assam and Calcutta, administration of opium to infants was rarely practised. In the United Provinces (Uttar Pradesh area), where opium is largely grown, the custom was prevalent in certain parts, and was showing signs of decrease in others.

From a rough general survey of different parts of India by these workers, it was found that, although opium was administered extensively to infants in some of the large industrial areas such as those of Bombay, Calcutta and the Uttar Pradesh, where women have to do long hours of work in factories, this custom was becoming progressively less prevalent. This was especially the case in the rural areas. It had entirely disappeared from many parts of India where it existed before and was rapidly disappearing from others. Even in industrial centres the doping of children with opium was rapidly diminishing. This was partly due to the educational work of infant welfare societies and partly to an increase in the price of opium. Indian mothers on learning the disadvantages and harm done by the drug to infants abandon the practice quickly. The belief that it was good for the babies' growth also rapidly disappeared as its evil effects were more and more impressed on the minds of the mothers. In Gujrat, Madhya Pradesh, the Maharashtra and the Deccan, where the custom was very prevalent at one time, an enormous decrease was recorded. Among the educated classes in cities and towns the custom has become extinct in most parts. In parts of Orissa, although the use of opium was very prevalent among adults, administration to infants was not common. In the Madras area this custom was also showing signs of decrease.

Doping of Infants

Investigation by Chopra and co-workers (1934) in the field revealed that the practice of doping infants with opium was generally begun during the first few weeks of the child's life, the earliest age being three weeks and the latest about three months. Occasionally, however, doping was started at a later age. In a series of cases examined by these workers it was found that in about 90% of infants the drug was started before the fourth week of their lives and that in only 10% it was started after this age.

In the rural areas, it appeared that the drug was always administered to infants who were weakly and ailing. Those infants who had no trouble during this period were rarely given the drug by the labouring classes. It was further found that the practice was generally discontinued when the child had attained the age of 2 or 3 years. A random sampling of a series of 100 infants showed that there was no child to whom the drug was habitually administered after the age of 3 years. There was, however, no hard-and-fast rule regarding the age when doping definitely stopped but the practice was generally given up when the child began to play about and could live on ordinary food such as rice, dal and vegetables.

Causes of Doping

For disease and minor ailments opium has always been considered a sovereign household remedy. As stated above it was specially given to children to allay diarrhœa during their teething period and the peevishness and salivation which accompanied it. There was a deep-rooted belief amongst the parents in many parts of the country that opium acted as a preventive against cough, diarrhœa, cold and other minor ailments. The palliative properties of the drug in these conditions cannot be denied, and the ignorant people considered it a necessity for their children and were generally quite unconscious of the harm it did.

A large number of parents started giving the drug on account of some minor ailments, and its frequent repetition led to its habitual administration to the children. The table below presents the principal causes for which the drug was started in 100 infants selected at random:

		Number of cases
1.	Cold with sneezing, coughing, watering of the eyes and nose	20
2.	Boils all over the body (called " charu " in the Punjab)	8
3.	Diarrhœa, particularly infantile diarrhœa with green stools	30
4.	Teething and other such troubles	10
5.	Colic and other pains	18
6.	Sore eyes, pain and watering of the eyes, otitis media with purulent discharge from the ear (opium is believed to dry up the discharge and allay pain)	10
7.	To cause loss in weight	1
8.	For polyuria and anuria	1
9.	For infantile convulsions	1
10.	As general tonic and euphoric	1
	TOTAL...	100

From the data presented above, it will be obvious that in 48% of the infants the drug was given as a cure for abdominal discomfort, diarrhœa, and colic; in 30% for the relief of catarrh of the respiratory passages and conjunctivitis, and in 10% of troubles associated with dentition. In only one child was the drug given because of its supposed virtues as a tonic.

Dosage : The dosage employed was generally very small and was said to be equal in weight to that of a poppy seed. Experience had taught mothers to keep the dose as small as possible, because infants usually develop tolerance to the drug very slowly. The dose was usually three-sixteenths to three-eighths of a grain (11 to 23 mgm) to begin with, and was gradually increased to obtain the desired effects; parents were likely to increase the dose whenever the child got an attack of some ailment such as diarrhœa, cold or cough. In the large majority of cases the dose was kept below one and a-half grains (90 mgm); in only a small percentage of children were large doses given.

The drug was generally administered twice daily, in the morning and evening in the form of crude bazaar opium. The usual practice was to buy a week's ration at a time and keep it in a small tin box. The size of about a pin's head was put into the mouth of the child, who was then put to the breast. In Bombay State, especially in Gujerat and Kathiawar, small pills were made which were given the name of *bala golis* or children's pills which were commonly sold by quacks. One of these was dissolved in a little water or milk and was given to the child. Sometimes, suckling mothers smear their nipples with opium and thus administer it to the infants.

Effects produced

The majority of the parents were unanimous with regard to the effects produced by the administration of the drug. They stated that, after the dose, the child becomes quiet, smiles, plays about for a while and soon goes off to sleep. When examined after the usual dose, these infants lay quietly sleeping or half-sleeping close to the spot where the mother was working. The narcotic effects generally last from 4 to 6 hours during which period the child remains undisturbed.

An important result of the practice is constipation. This, however, is desired and encouraged by the parents to save themselves the trouble of cleaning the child frequently. The general physical condition and health of the majority of the children examined was poor, but it is difficult to say how far this poor state of health and physique was due to the effect of opium, and how far to other causes—viz., insufficient nutritious food, unhygienic surroundings and general lack of care. There was no doubt, however, that, as compared with other children under similar circumstances who were not getting the drug, the children doped with opium looked leaner and more unhealthy.

The parents in many places fully believed in the beneficial effect of giving the drug to their children. This belief, they said, was based on the accumulated experience of many successive generations who had used the drug. The harmful effects of opium such as constipation and intoxication, which may be considered as the cause of poor health, were actually regarded by the parents as being beneficial and health-giving. There is no doubt that, despite the large doses they were receiving, some of the children did look quite healthy, but such cases were not common.

Deaths from over-dosage undoubtedly did occur but were very rare. Continued use of the drug appears to make the child more liable to attacks of epidemic diseases. Most of these children, enquiries showed, were constantly ailing and the mortality rate amongst them was comparatively high.

It was observed that children soon get addicted to the drug. If the dose was not given about the due time, crying, watering of the nose and eyes, refusal to take nourishment properly, and diarrhœa were the principal manifestations. All these symptoms subsided rapidly when the proper dose was given.

Physical Effects

Opium appears to hinder the normal growth of the child, probably on account of the attendant toxæmia. The children examined were as a rule small for their age, thin, anæmic and emaciated; their conjunctivæ were dull and pupils contracted. Conjunctivitis, corneal ulcers and opacities, otitis media with purulent discharge were frequent. About 40% of the children were found to be suffering from enlarged tonsils, adenoids and discharge from the nose. The tongue was often thickly coated, the abdomen protuberant on account of sluggishness of bowels and accumulation of fæcal matter and production of wind. The liver was often enlarged and palpable. All of them had a relaxed skin on account of paucity of subcutaneous adipose tissue and they were mostly under weight. The bones were prominent owing to wasting of the overlying muscles, and the chest was thin-walled and ribs prominent on account of wasting intercostal muscles. The cardiac impulse was forcible and the heart-sounds loud, often being audible all over the chest.

Weaning from Opium

The habit does not have the same hold over children as in adults, and in most cases the drug can be stopped without great inconvenience. The weaning of the child from the habit is generally done gradually and any resumption of it in later adult life is entirely disconnected from the use of the drug in childhood. When for want of a dose the child cries or becomes restless, a heavy meal of rice or milk stops the discomfort. The period taken for the complete withdrawal of the drug varies from a few weeks to one or two months. Irritability resulting from discontinuance of the drug is effectively controlled by the administration of two or three minims of tincture of belladonna with two to four grains of potassium bromide. The child is quieted down at once and may fall asleep.

It will be seen from the above that the reasons underlying the doping of children with opium in the large majority of infants were connected with belief in its quasi-medical properties.

Chapter VI

Quasi-medical use of *Post* (unlanced capsules of *Papaver somniferum*)

Poppy Capsules

There is little doubt that the merits of seeds of the opium poppy as a food were recognized much earlier than the somniferous property of the capsules. It is also certain that the soporific and narcotic properties of the capsules themselves were appreciated long before their recognition in its milky sap. The capsules have been employed in the preparation of soporific drugs or in the preparation of stimulating and soothing beverages from time immemorial. According to Watt, *Papaver somniferum* was grown in Asia Minor many centuries ago for its capsules, and the Arabs carried the dried poppy-heads to the Eastern countries including China even before the inspissated juice was taken and its properties made known to the inhabitants of those regions. The medicinal properties of the plant and its capsules were fully known during the early classic period of Greece and Rome. There are records to show that the Arabs instructed the Chinese to prepare from these capsules a soporific beverage and medicine before they knew anything about the properties of opium.

It will thus be seen that capsules of the poppy aroused the attention of the human race long before opium was known. Little wonder, then, that, after their narcotic and soothing properties were appreciated by those practising the healing art, they became known to the laiety who also made use of them for satisfying the almost universal desire which human-beings possess for a stimulant or a sedative.

Medical uses of poppy capsules. The capsules have been used in both the Ayurvedic or the Hindu medicine and the Tibbi or the Mohammedan medicine for many centuries as a sedative both for internal use and external application and are still used.

The " Hakims " or practitioners of Tibbi medicine prescribe them for headache, diarrhœa, dysentery and digestive troubles in children. They are used as a household remedy in many parts of India and are given during the teething periods by mothers to their children to keep them quiet. An infusion prepared from the poppy-heads is used as a soothing application for bruises, inflamed, excoriated and swollen parts. It is also used as an application for various forms of painful conjunctivitis, inflammation of the ears and other similar conditions. Fomentations with poppy-heads are even now applied to painful inflammatory swellings.

In China the physicians used poppy capsules freely in the early centuries of the Christian era. Most of the Lung dynasty medical writers extol the merits of poppy capsules, especially when combined with astringent drugs in the treatment of dysentery. The Chinese writer Wang-Shih, in his work *I-Chien-Fong*, says the effect of poppy capsules in dysentery is simply magical. Both the red and white forms of poppy were certainly described and used in the Chinese medicine in the 11th century before opium was known. A medical author of the Yuan dynasty (13th century) describes the preparations of poppy capsules as being a very effective remedy against dysentery.

Use as a beverage. Whatever may have been the case in the countries of its origin (e.g., Asia Minor), there appears to be little doubt that poppy-heads began to be used not only for their medicinal properties but also for euphoric purposes in India soon after the introduction of the poppy plant in the country. The plant was known as " Koknar ", the capsules were called *goza*, *khol-i-koknar* or *post-i-koknar* or simply *post* or *post doda*. In the time of the Moghuls a beverage made from the poppy capsules known as *Kuknar* was very commonly used throughout the country.

The beverage *post* is prepared by soaking the poppy capsules overnight or for five or six hours before use. These become quite soft and are then rubbed between the fingers in a small quantity of water till they are broken up to pieces. This process takes a long time and those who take the beverage enjoy this. In this way any alkaloid present in the capsule passes into water. The whole mass is then strained through a piece of cloth and squeezed till all of the solution comes through. This is then suitably diluted or mixed with sugar and forms the beverage.

According to Watt, the beverage *post* at present taken in the Punjab closely resembles *Kuknar*, which was a luxury among the Mohammedans in the time of Akbar. We have already referred to the beverage known as *Charbughra*, which was a mixture of wine, hemp, opium and poppy capsules. Many other references in the Moghul literature indicate the extent to which the habit of drinking *post* or *Kuknar* prevailed among the Indians during the 16th century and later. In the history of the Punjab during the time of the Sikhs there are many references to the use of the beverage, but it is not possible to know the extent to which it was habitually used. Since the introduction of restriction to the cultivation of the poppy, the temptation has been undoubtedly removed from the doors of the peasant and the habit has considerably decreased. Poppy-heads are obtained now with difficulty and in most parts of India the beverage *post* or *Kuknar* has become unknown. The use of poppy capsules or *post* even in indigenous medicine has become uncommon in this country.

Alkaloidal content of capsules. Since the quantities of alkaloids obtained from the capsules from which opium has not been extracted are so small as to be of no commercial value, no detailed analysis of these appears to have been done. Lyon of Bombay (1879) analysed poppy capsules from Malwa. He obtained 0.099% of the alkaloids soluble in ether, consisting apparently of narcotine, 0.023% of impure alkaloids soluble in benzol, and 0.033% of impure alkaloids soluble

in chloroform. No morphine apparently could be detected by the ordinary reagents.

Chopra and co-workers (1931) carried out a detailed analysis. One hundred and thirty-seven grammes of the powdered capsules gave 15.18 grammes of the alcoholic extract. This contained 1.05 gramme of the total alkaloids of which only 0.045% (or 0.673 grain) was morphine. About 50 to 60 capsules weighed 137 grammes and contained a total alkaloidal content of 1.05 gramme. The average dose is 5 to 10 capsules, which will mean about 1 to 2 grains of the alkaloids in each dose or 3 to 5 grains a day. This quantity would be quite sufficient to produce the effects for which the poppy-heads are taken.

It will be seen from these results that the poppy capsules contain a very small quantity of morphine and large quantities of narcotine, papaverine, codeine and other alkaloids which have a decidedly weaker depressant action on the central nervous system. The combination of alkaloids probably strengthens the effect of individual alkaloids.

Habitual use of capsules. In a study of 530 cases of habitual use of poppy capsules studied by Chopra (1930) it was found that the addicts generally belonged to the lower grades of society, the majority of them having very meagre means. Those belonging to better classes were few in number and were generally those individuals who had tried a number of narcotic drugs such as hemp drugs, opium, alcohol, cocaine, etc. An inquiry made in the Punjab showed that most of the addicts were Muslims belonging to lower classes whose main occupation was agriculture. A number of addicts belonged to the menial classes such as sweepers, water-carriers, hackney-carriage drivers, etc. No particular cause could be assigned as to why they became addicted to poppy-heads except that they were obtainable and that they were cheaper than opium.

The average dose of poppy-heads estimated from a large series of cases studied worked out to be 3 ounces per day. This was generally divided into 2 or 3 portions and taken morning and evening or in the afternoon also. About 8 to 10 average-sized capsules weighed about 2 ounces. A capsule when lanced gives about half-a-grain of opium on an average but we have already pointed out that, when the capsules from which opium has not been extracted are ripened and dried, they neither yield the same quantity nor the same quality of alkaloids. An average dose of poppy-heads, however, contains sufficient alkaloids to produce the effect which the drug produces. There were people who took as much as 16 to 20 ounces of capsules a day but this was very rare. As a rule the dose was kept below 10 ounces, by far the large majority taking between 2 to 4 ounces, equivalent to 3 to 6 grains of the alkaloids.

Quasi-medical use of post leads to habitual use. In the series of 530 *habitués* referred to above as many as 40.3% took this drug for some disease or ailment which it was believed to cure. It was interesting to note that out of 214 cases who took the drug for some illness, the majority kept to very small doses of under 2 to 4 ounces. The commonest ailments for which the drug was taken were, in order of frequency, eye diseases, diseases of the respiratory system such as asthma, hæmoptysis, cold, cough, etc., aches and pains and finally the bowel diseases. It is evident that poppy-heads have never been taken for any serious disease.

Those who take *post* beverage habitually are very fond of company and always like to have friends or associates around them when taking the drug. They advise *post* as a panacea for all possible ailments and troubles. Most of them had contracted the habit by advice and even entreaties of other addicts who had derived benefit for some ailment or disease.

Effects produced. The symptoms and effects produced by opium and poppy-heads differ more in detail than in general aspect. They naturally differ with the dose taken, the duration of the habit and the idiosyncrasy of the user. On the whole it may be said that the effects of the capsules are milder and not so lasting as those of opium and for this reason capsules have to be taken more frequently. Poppy-heads contain morphine and codeine, and narcotine and papaverine in about equal proportions, but the amount of morphine itself is very small as compared with that in opium. Although most of the opium alkaloids depress the psychical areas, the action of morphine in this respect is much more powerful and the same is true of its analgesic effects. In fact papaverine, narcotine, and also codeine to some extent, act more as excitants than depressents and their stimulant action, especially on the psychical areas, appears to be a prominent feature of indulgence in *post* after its use is started for medical and quasi-medical purposes.

Within a few minutes after taking the potion, a feeling of ease, comfort and well-being is experienced. There must be some psychical element in this as the alkaloids would probably take 10 to 20 minutes at least to be absorbed from the gastro-intestinal tract into the circulation in sufficient quantities to produce their effects. There is undoubtedly a marvellous change in the individual soon after the potion is drunk. From a condition of lethargy, fretfulness, moroseness and peevishness, he passes into a state of gaiety and talkativeness. He looks happy, becomes very communicative and companionable. This state of affairs lasts for 1½ to 2 hours and gradually the agreeable feeling of elation passes into a state of depression, the person becomes drowsy and may fall off to sleep. The stage of depression is not nearly as marked as in the case of opium. The effects completely pass off in 5 to 8 hours. The excitement stage is undoubtedly more pronounced than with opium. The effect appears much more quickly, probably owing to the fact that the alkaloids are taken in solution and are absorbed more rapidly.

When the habit has established itself for a long time the *habitué* generally looks dull and sleepy, becomes slow of comprehension and inattentive. His gait becomes heavy, his movements slow, he is careless in dress and dirty in his habits. His speech is slow and hesitating, in monosyllables, jerky and his voice is husky as if he were talking in sleep. The only time when he brightens up and looks his normal self is when he has taken his potion, and for 2 or 3 hours afterwards. Even then his method of talking gives him away. He speaks as if in a dream; he pays little attention to what is said to him but goes on muttering to himself. The special senses are not directly affected but appear to be disturbed through impaired attention or heightened reflex irritability.

Even small doses—e.g. 5 or 6 capsules a day—appear to produce a marked physical deterioration when continued foe prolonged periods and the addict becomes mentally degeneratr and lazy. Probably the chronic constipation which is present in the majority of these individuals and the consequent intestinal toxæmia have a great deal to do with it. Even those addicts who took small doses could carry out their ordinary vocations only with difficulty.

The addicts say that poppy-heads do not upset their digestion, in fact they claim that it sharpens their appetite and they can eat more and digest better. They claim that their eyes feel dry, the sight is improved and cough and expectoration are decreased. It is said to dry all the excessive secretions. Some claim that it gives them relief from asthma. A drink of *post* in the evening after a hard day of toil refreshes them and gives them ease of mind and languor of the body.

Those who take capsules habitually are generally believed to suffer from sluggishness of the bowels and chronic constipation. The act of defæcation thus becomes difficult, so much so that the addicts sit for long periods and forget that they are in the act of defæcation. Constipation, however, does not appear to be so frequent in those who take *post* habitually as in those who take opium. The drug undoubtedly has a well-marked diuretic effect and those addicted to it micturate very copiously and frequently.

Habitual use of *post* makes the individual forgetful not only of himself but also of his surroundings. He appears to lose all idea of correlation of time and space; he forgets his environment and does not know what he is engaged in doing. He may sit in one place for hours together doing nothing, without feeling it. He may walk a few yards and think that he has travelled for miles or he may have walked for miles and think that he has walked only a few paces. He may go on doing hard work for hours without feeling it or he may sit idle for long periods. He loses the idea of correlation of touch, perception and localization and many stories are told about it. He is likely to become mechanical or automatic in his actions and appears to have no will-power. Once he starts doing a thing he will go on till he is reminded that it is time he stopped.

Physical, mental and moral effects. Habitual use of poppy-heads produces considerable psychical, mental and moral degeneration. In the Punjab a lazy, slovenly, dull and unintelligent-looking person is often called a *posti* (or one who indulges in poppy capsules). The *habitués* who have taken the drug for prolonged periods are, as a rule, spare and emaciated individuals with stunted growth and subnormal weight. They have a sallow, muddy appearance, sunken eyes and cheeks and are anæmic. Their eyes look dull and sleepy, they have heavy palpebræ and conjunctivæ. Advanced cases who have taken large doses look cachectic, have a dirty tongue, foul breath and give the impression of suffering from chronic intestinal toxæmia. The subcutaneous fat is absent and the muscle tissue is wasted so much that the dry skin becomes quite loose over it. The throat is dry, respirations are slow and shallow and the expansion of the chest is impaired. The pulse at the wrist is weak, slow and compressible; soft hæmic murmurs are not infrequently audible over the heart.

The mental effects differ somewhat from those of opium. The excitement stage is more prolonged on account of the smaller amount of morphine and larger quantities of the alkaloids narcotine and papaverine. There is a feeling of elation, exuberance and well-being, which manifests itself in speech and gestures. In this stage the addicts become very communicative and reveal all their secret thoughts. There is loss of responsible control over the mental processes, but the control of movements is not impaired as is the case with alcohol. The net results of the action on the psychic areas is unrestrained imagination which may take different directions in different individuals. In some it will produce excitement, in others drowsiness and sleep. The irritation of the nerve cells produces hallucinations which, though present in this addiction, are not so prominent a feature as in the case of cocaine. The effect on the addict who has taken the drug for long periods resembles a chronic poisoning of the nervous system, especially of the higher psychical areas, which alters the mental activity from a state of high irritation to a complete breakdown even to paralysis. The individual becomes dull, lazy and careless; he has a vacant look and his eyelids droop; the temper is often irritable and he gets excited quickly; his will-power and determination of mind and character are weakened. The addicts are generally feeble-minded individuals and are untruthful, selfish and self-centred.

Chapter VII

Smoking of opium in India

NOTE. — Although opium-smoking is not quasi-medical use within the usual meaning of this term, it has been considered advisable to include this chapter on opium-smoking in order to provide a comprehensive survey of all uses of opium other than those made with medical aid—i.e., other than consumption for strictly medical purposes. See also page 17 and especially the footnote on that page.

Introduction into India. Even up to the beginning of the 19th century no writer has recorded the smoking of opium in India, although it prevailed in China. Tobacco-smoking was introduced into India after the 16th century and it is not evident that, in the case of India as of China, opium-smoking was simply an outcome of tobacco-smoking. It is uncertain how this habit was brought into India but, fortunately, it never assumed such a menacing aspect as it did in China. The Royal Opium Commission of 1893 described the habit as " comparatively rare and novel " in India.

A careful consideration of the available data points to the possibility of introduction of opium-smoking in India by Mohammedan traders from Persia and Afghanistan. The stimulating and the narcotic properties of the drug, combined with the wonderful flow of ideas which occur early in the act of smoking, appealed to the easy-going, well-to-do section of society and the habit spread among them, particularly during the days of decline of the Moghul Empire. The habit of smoking opium, however, began to be considered disreputable and no self-respecting person would own to it. Besides, during more recent times restrictions were placed on it by law, and both these factors made an accurate survey of its incidence very difficult.

A study of the records, however, leaves little room for doubt that opium-smoking has always been an uncommon practice in India. That it did exist and does exist even now among certain classes is evident from the fact that the word " chandubas " or opium smoker is well known, and in some of the old Hindustani books very detailed and a somewhat exaggerated description is to be found of this habit and the effects produced by it. Opium dens were found till quite recently in many of the large towns in India, but the proportion of people who smoked the drug was very small. Its incidence among the people was very irregular and, although there were areas and certain classes of the population who were badly affected, these fortunately formed a very small minority.

Investigations in the field by Chopra and co-workers (1938) showed that the habit of smoking opium in one form or other was met with on a small scale in many of the large towns in India. The practice was almost entirely confined

to the poorer classes. It may be stated here without fear of contradiction that the habit of opium-smoking has considerably decreased in India during the last 40 years and as a result of stricter control measures may now be considered as almost eradicated. Opium-smoking, however, appears still to be practised in secret in some of the large towns among the lower strata of society.

Causes leading to opium-smoking

A large proportion of the habitual smokers studied by Chopra and co-workers (1938) in the tea gardens and forest areas in Assam and in the Central Provinces said that they took to opium-smoking because they had to perform strenuous work in an unhealthy climate. They believed that opium had a general stimulant action and increased their vigour and working capacity. It also kept off hunger and fatigue. These beliefs were responsible for the spread of the habit amongst the labouring classes in some of the tea gardens and the forest areas.

Race. Among the Mongolian races there appears to be a strong instinctive desire for a stimulant, and drugs possessing euphoric properties appear to have great attraction probably because, *inter alia*, they have the reputation of having aphrodisiac properties. The racial factor was in all probability responsible for the higher incidence of opium-smoking in Assam and Burma as compared with any other part of India. The high incidence in Madhya Pradesh was, however, difficult to explain.

Diseases. Sufferings produced by disease conditions are very commonly blamed for the habitual use of opium. The role of the disease factor was studied in detail in one series of smokers. This factor was present in more than one-third of one hundred smokers investigated. In a hot humid climate, such as is met with in Assam, where the incidence of cough, asthma, dysentery, typhoid, malaria, kala-azar and bowel infections was high, there was a widespread belief that the regular use of opium, whether by smoking or eating, acted as a prophylactic against, and also as a cure for, these diseases. On account of the power this drug possesses of depressing the respiratory centre, the irritative cough is certainly ameliorated. The effects upon the gastro-intestinal tract, particularly in diarrhœa and dysenteries and painful affections already referred to are rapid and very striking. In this series of cases, diseases of the respiratory system such as cold, cough, coryza, asthma, hæmoptysis, etc., were the commonest exciting causes of smoking opium. Next in order of frequency were aches and pains, such as sciatica, neuralgia, rheumatic troubles and fevers. Belief in its general tonic effects and its power of controlling symptoms of bowel diseases were minor exciting causes for indulgence. In most cases the use of the drug was often started by suggestion at the instance of a smoker and in no case was it begun on the advice of a qualified medical practitioner.

Fatigue and hard work. In quite a number of persons the habit was started to enable the addict to bear the strain and stress of hard work. In a number of others opium-smoking was started as a substitute for such habits as alcoholism and addiction to cocaine. These addicts stated that a few whiffs of opium satisfied their cravings for cocaine and alcohol and therefore the desire for these drugs was minimized with comparatively smaller doses of opium. All these individuals were weaklings of vicious temperament who were given to multiple drug habits and excessive drinking. The reason for substituting opium-smoking often was that they found it less expensive than cocaine or alcohol and as much if not more satisfying.

Association. The opium smoker should be regarded as an individual who acts as a focus of infection for susceptible individuals. In India ordinarily it is difficult to obtain prepared opium for smoking purposes, but once the acquaintance with habitual smokers is developed, ways and means of securing these preparations are found. The smokers as a rule do not reveal the names of the manufacturers and distributors of these preparations. When the habit is confirmed, the new consumer realizes his helplessness espêcially if he has had the misfortune of running short of the drug and experiencing the symptoms of sudden withdrawal. Very often he himself starts manufacturing these preparations and keeps a supply in hand in case of emergency. A smoker may have no money for his daily food, may be insufficiently clad, yet will manage to get his dope, as this is the only method of escape from the acute mental and physical sufferings produced during the period of abstinence. He will pawn or sell his personal belongings and those of his family and will try to get the drug even if he has to sacrifice all that he possesses in the world. The ravages caused by the habit in such persons are terrible and the moral depravity produced is indescribable.

Preparations used for smoking

The excise opium as it is sold in India in licensed shops is not suitable for smoking purposes. It is therefore necessary to convert it by certain manipulations into suitable preparations. This process requires certain equipment and takes a good deal of time. This fact is probably responsible for the existence of opium-smoking dens, as it is there that opium for smoking is prepared and sold.

In India two preparations of opium are generally used for smoking. These are *madak* and *chandu*. A third preparation which is rarely used in this country is opium dross.

Madak is much more extensively used in India than *chandu*, and in most parts of the country this preparation is smoked. Madak is prepared by mixing raw opium with water, which is then heated to boiling-point. The boiling is continued till a thick suspension is formed, impurities occurring in form of scum being removed. This is then strained through a cloth and mixed with charred leaves of *Acacia arabica* till it assumes the consistency of a thick paste. The mass is then rolled into pills which are available for smoking.

Chandu and chandul or clarified opium. This is a stronger preparation and was only used in India by persons who were heavy smokers, or by the Chinese smokers settled in this country. Chandu is prepared by boiling a strained solution of opium in water in a copper vessel till it becomes thick in consistency. As the concentration proceeds crusts form on the surface of the simmering mass. These are removed as they form, until finally a thick mass of the consistency and appearance of coal-tar is obtained. This is the " smokeable extract " and is the chandu or chandul of opium smokers. The chandu commonly smoked is often adulterated by addition of dross scraped from chandu pipes which has a high morphine content.

Opium dross. Opium dross is the residue left in the pipe when either chandu or madak is smoked. The quantity of the dross produced depends on the type of pipe used and the method of smoking employed. Usually the amount of dross

produced corresponds to a maximum of 60% and a minimum of 40% of the quantity of the prepared opium smoked.

The dross is usually prepared for smoking by mixing it with water and subjecting it to heat till it assumes a thick consistency. This prepared dross is smoked in the same way as prepared opium and leaves a residue in the pipe which is called second dross (in the Netherlands Indies *dit-jingko*). The second dross is often consumed in very much the same way as the original opium dross. It is generally believed that the smoking or ingestion of dross is more harmful than the smoking of prepared opium. The reason for it is not known, but it is possible that the high alkaloidal (morphine) content of this substance is responsible for this belief.

Modes of indulgence. Different kinds of apparatus have been improvised in various parts of the country for smoking opium. The one commonly used consists of an elongated wooden pipe, made from bamboo or desert acacia, 12 to 18 inches in length and three-quarters of an inch in diameter. One end fits into a small china or earthenware bowl, and the other end is the mouthpiece.

This method of smoking madak is simple. The bowl is slightly warmed and the madak pill is placed in the bowl. A glowing charcoal is applied and simultaneously several pulls are made through the mouthpiece, the smoke being deeply inhaled into the lungs.

When chandu or clarified opium is smoked, the technique is somewhat different. The bowl is at first warmed by holding the pipe over the brazier so that the mass of opium placed in it becomes sticky and begins to melt. The temperature to which the bowl is heated is of importance because if it is too high there is danger of the opium melting rapidly, becoming charred, and emitting a disagreeable odour. After the bowl is properly warmed, a small piece of chandu or clarified opium is placed on one side of the hole leading into the pipe or just over it. In the latter case a hole is made through the opium mass with a stylet. The bowl is again warmed and, as the opium softens, it is stirred with the stylet until it forms a thick coffee-coloured mass. A piece of glowing charcoal is then held with pincers close to the opium and the smoker applies his lips to the other end of the pipe. When the opium is on the point of melting, he actually places the burning coal on it, and gives a few rapid and deep pulls inhaling the smoke into the lungs. The actual process of smoking lasts less than a minute, and then more opium has to be taken if it is desired to continue smoking. The smokers inhale the smoke deeply and after each pull at the pipe, sweet food, such as bananas, sugar-cane or sugared tea, is often taken.

Classes of opium smokers. Three classes of Indian opium smokers may be described:

(i) *Occasional smokers.* This class is ordinarily addicted to opium-eating, but indulge in a smoke, a pull or two of madak or a few whiffs at a chandu pipe occasionally when an opportunity offers itself, for example when they are in the company of opium smokers. These persons are as a matter of fact aware of the evil consequences of over-indulgence and have enough will-power to limit the amount of smoking. Properly speaking these individuals are not active smokers, but may be potential ones who may take up the habit any time when they have sufficient means or their will-power is weakened.

(ii) *Regular but moderate smokers.* The majority of the addicts in this group are from the artisan class, such as hackney-carriage drivers, domestic servants, labourers working in tea gardens and forest areas, etc. These persons smoke once or twice a day and usually consume up to 20 grains a day as their means permit. Many of them earn a few rupees or so per day and spend a large amount of their earnings on their dope. They generally smoke in the evening after the day's hard labour is over. The smoking is mostly done in their own homes, but it may also be indulged in a regular opium den on a holiday. Such addicts are now decreasing in number and in the series studied formed about one-third of the total number.

(iii) *Regular and excessive smokers.* This class was much more numerous formerly than the preceding two classes and comprised more than two-thirds of opium smokers studied by Chopra and co-workers. The dose in this case ranged from 20 to 180 grains a day. Most of these addicts belonged to the lower and mendicant classes who had meagre means but obtained money by begging. A few belonging to better classes were generally individuals who had tried all narcotic drugs, such as ganja, charas, opium, alcohol and cocaine, etc. and wanted something more potent. Not infrequently the excessive smokers were morally degenerate and, when they had no money for their usual smoke, resorted to begging and thieving.

In spite of the stringent restrictions placed by law, opium smokers prefer to smoke in company. The smoker feels happy while he is watching others and is watched by others. All sit on the floor or on a platform. Social distinctions disappear and the smokers take part in the ritual of preparation in the most leisurely fashion and with much good humour. Tea and sweets are brought in and served to all present. The glowing of the brazier and the manipulation of the pipe are kept up with the utmost relish and enjoyment. All combine to make the sitting as pleasant as possible; there is no hurry and no thought of anything else. This is the sort of " atmosphere " the smokers like to secure even though they may be in the dark corner of some smoke-blackened opium den.

Semi-religious and social aspects of the habit. Smoking of opium was not an uncommon practice in the old days at such social gatherings as marriages and funerals in certain parts of Assam. The custom required that opium should be distributed among the smokers who were present on such an occasion. Not long ago a ceremony purporting to be of a semi-religious nature, the *Kenia seba* (the serving of opium), was found to exist among the more ignorant classes in Assam at which opium addicts assembled and opium was distributed with the object of averting sickness or other troubles sent by Providence. The distribution and consumption of opium was also common at *namagoa* (the name-giving ceremony). These semi-religious uses of the drug were purely the inventions of interested opium consumers and had no authority from the *Sastras* (religious books). They were looked upon with disapproval by the better classes and have now practically entirely disappeared.

Madak-smoking as a social function in Assam existed formerly on a much more extensive scale when opium was not only more easily available but was much cheaper in price. Certain families were said to have been ruined by the habit. The number of smokers declined rapidly as opium got dearer and restrictions against smoking were increased. Opium-eating was found to be cheaper and less troublesome and many smokers took to opium-eating instead.

Owing to restrictions placed during recent years on smoking opium, the opium dens in this country have practically entirely disappeared.

Control of the opium-smoking habit by the Government. It has long been recognized that in India opium-smoking stands on a different footing from opium-eating. Opium-smoking was indulged largely for its euphoric or pleasure-giving effects, and was certainly a social vice. The danger of its spread, when practised in public, furnishes strong justification for adopting strict measures which approach as nearly as possible to total prohibition.

In 1925, under the agreement arising out of deliberations of the First Geneva Opium Conference of the League of Nations, India was bound to take measures to reduce the consumption of prepared opium so that it would be completely suppressed within 15 years. Prepared opium was defined as any product of opium obtained by a series of operations designed to transform it into an extract for smoking purposes. Even before this conference, according to the Hague Convention of 1912, all Provinces of India were under an obligation to suppress opium-smoking. In Assam and other Provinces an Opium-smoking Act was in force, which prohibited the smoking of this drug.

Under the existing law, smoking is subject to very severe restrictions. The sale of the preparations of opium for smoking purposes is absolutely prohibited throughout India, while their private manufacture is allowed only to the smoker himself or, on his behalf, from opium lawfully in his possession, and to the extent of 180 grains (one tola) at a time. The quantity of opium daily used by an opium eater and the inconvenience and difficulty involved in the repeated preparation for the smoking are so great that these restrictions practically amount to total legal prohibition.*

Effect of Opium-smoking

In persons who have just started smoking opium, the symptoms produced are those of euphoria. At the onset the senses become momentarily keen; the stimulant effects are produced by the first pull; physical pains of whatever nature disappear or become abated; there is a feeling of elation, followed by a delightful languid ease, an exalted sense of superiority and later on, sleep with pleasant dreams. As smoking progresses the smoker becomes dull and drowsy. If at this time he receives some important and exciting news, he takes little notice of it and indulges in another smoke. Soon after he has finished the first pipe the smoker becomes talkative and communicative. He talks of politics, religion, poetry, and other subjects of special interest to himself. Facts are often exaggerated and he is over-confident of his powers and superiority. He talks mostly of his personal affairs and thinks that he is logical in all his expressions and conclusions. He is disposed to criticize others and is anxious to prove all sorts of fantastic theories in order to impress his hearers, who are generally smokers themselves, and who listen attentively. Time is of little consequence. The smoker becomes a slave to the habit and the evil is enhanced by the bad surroundings in which the habit is generally indulged in.

Early stages of habit. As the habit takes root the individual gradually becomes conscious of the danger and ill-effects of the practice. Attempts and efforts are often made to give up the habit and a constant struggle seems to be going on between the sense of caution on the one hand and the desire for euphoria on the other. The symptoms produced are similar to those produced in the first group, but are less marked. There is a general attitude of hesitation during this period and the habit is continued partly because of its pleasure-giving symptoms.

The stage of established habit. Prolonged use of the drug is apt to produce permanent changes in the system. The mental and moral faculties are affected and the addict behaves more or less like an abnormal individual. After the drug is smoked, the symptoms of incompetency and inhibition present during the abstinence period completely disappear. The drug, however, is able to produce only a temporary sense of well-being, and no marked euphoria or intoxication, as is seen in the first two stages. Addicts at this stage have a desire to give up the habit but are unable to do so on account of the dread of the withdrawal symptoms.

Long-standing habit. The confirmed addicts, if they do not change their mode of consumption, are apt to get into a stage of cachexia or inanition. The mental and physical changes are much more marked in this group than in the previous three groups. The physical changes may go on to actual dementia. The individual is pale, thin and commonly subject to intercurrent diseases. The craving for the drug is greater than ever. When the drug is smoked by such individuals the euphoric symptoms are absent. The only effect produced is a short-lived feeling of normality after indulging in a smoke. The feeling of constant and general depression always present is overcome for the time being. If smoking cannot be indulged in at the proper time there is great prostration, vertigo, torpor, watery discharge from the eyes, acute distress and insomnia. All these feelings are overcome for a while by the smoking of a single pipe of opium.

Chapter VIII

Opium consumption in India for quasi-medical purposes—present situation

In 1948 the Government of India agreed to restrict the production and use of opium in the country (see Chapter I) and this marked the beginning of what we have called the third phase.

From what has been stated in previous chapters, it is obvious that the underlying causes leading to the use of opium by the people of India, in the large majority of cases, were belief in its quasi-medical properties. Owing to inadequate facilities of medical relief in the past, it is not surprising that the wonderful pain-relieving and other qualities of this drug led people to make use of it in some form for the relief of various ailments. During the last decade, however, medical relief to the population both in the urban and in the rural areas in most of the states has been greatly extended. This has led to a significant decrease in the consumption of opium all over the country. This is clearly shown by the consumption figures given in the following table.

Year	*Consumption*
1948/49	376,489 pounds approx.
1949/50	301,432 " "
1950/51	320,169 " "
1951/52	296,974 " "
1952/53	271,395 " "
1953/54	209,767 " "

* *Note by the Editors :* The total figure of registered opium smokers given in the Annual Report of the Government of India for 1954, made under the 1931 Convention, was 2,519.

The *All-India Opium Conference of 1949* resolved that the use of opium for other than medical and scientific purposes should be totally prohibited and also that the quasi-medical uses of opium are not desirable and should be stopped as early as possible. It was further resolved that the central and state governments should " in any case, before four years, take effective steps to bring down the *per-capita* consumption of opium to a level not exceeding the League of Nations limit " which works out at up to 6 seers (12 lb.) for every 10,000 of population. These recommendations are being gradually put into effect everywhere and the consumption of opium both as an intoxicant and for quasi-medical purposes has shown a remarkable decline. This is clearly shown by the figures of consumption given in the above table. These figures show that in the five-year period between 1948/49 and 1953/54 a reduction of about 45% has already been achieved and, taking India as a whole, the consumption of opium per 10,000 of population has been reduced to well below the 12 lb. per 10,000 population standard laid down by the League of Nations. Smoking is prohibited (except for the relatively small number—2,519 in 1954—of registered smokers). In urban areas where medical facilities are constantly increasing, opium is now allowed on medical prescription only. Adequate machinery has been set up by the individual states to enforce this rule.

In such rural areas where medical facilities are still inadequate the quantity of opium used for quasi-medical purposes is being rapidly reduced by reducing supplies to the licensees and retail quotas to individuals.

Another important fact, which should be appreciated, is that consumption of opium varies enormously from state to state in the Union. *Per-capita* consumption in India, during the year 1947, was 7.68 grains against 9.25 grains or 6 seers per 10,000 of population, the standard fixed by the League of Nations many years ago. The consumption in India as a whole, therefore, is reasonable and does not exceed the League of Nations standard for the medical and scientific needs of the population. The table given above shows that, taking India as a whole, the *per-capita* consumption dropped to only 5.3 grains in 1953/54. The League of Nations standard was of course based on consumption in Western countries, where opium is almost entirely used in the form of medicinal preparations.

As far as the Indian Union is concerned, there are certain areas such as Madhya Bharat, Rajisthan, Patiala and East Punjab States where the *per-capita* consumption is still considerably above the League of Nations standard. With the progressive cut of 10% in the supply of opium made to these states from the government factories, it will be possible to reduce the consumption of opium in these areas to the standard of the League of Nations within a reasonable period. In fact a good deal has already been achieved in this connexion.

It is also significant that the Government of India is now strictly controlling the cultivation of the opium poppy by confining it to limited areas, where strict control can be and is being exercised. The opium produced by licensed cultivators goes to the two government factories at Ghazipur and Neemuch, where supplies of both alkaloids and excise opium are made. The opium factories in Madhya Bharat, Rajisthan and Doda (Jammu and Kashmir) have already been closed or are being closed down. The areas in the Punjab, where poppy was grown for the production of poppy-heads (*post*), are also under strict control and attempts are being made to stop this altogether within a specified number of years. This will put an end to the use of *post* for quasi-medical or other purposes.

Legislation with regard to the control of the sale of opium is being enforced uniformly in different states. The Dangerous Drugs Act, which is an all-India legislation, is being strictly enforced, and this in itself is operating as a potent factor in reducing consumption.

It has been made abundantly clear in the preceding chapters that in the vast majority of cases the use of opium is started on medical or pseudo-medical grounds, and it is due to the particular habit-forming properties of opium that such use, in a substantial proportion of cases, leads to confirmed addiction. Now that opium is no longer being made available for quasi-medical purposes and its price has been further increased, it is expected that addiction to the drug will rapidly decline and will soon cease to exist as a public-health problem. The few areas throughout the country where the use of opium is still comparatively widespread are being energetically dealt with by means of stricter enforcement of legislation, more extensive educational propaganda and provision of further medical facilities. The problem of the consumption of opium in India as it existed before 1948 is rapidly disappearing.

Chapter IX

Physical, mental, moral and social effects of the opium habit

Chopra and co-workers (1935) carried out a systematic statistical investigation into the physical, mental, moral and social effects produced by the habitual use of opium. In a study of a series of 1,523 cases from both rural and urban areas and from among people in different vocations and situations in life, an effort was made to evaluate the subject from the following points of view:

1. To what extent was the habit of eating opium responsible for the deterioration of the physical condition of the individual?

2. To what extent did the habit lead to intellectual, moral and mental derangement or decay?

3. What were the individual's social reactions? Did he remain a useful member of society or not?

Such factors as dosage, duration of the habit, individual tolerance, idiosyncrasy, social position and personal hygiene, exercise considerable influence upon the intensity of the effects produced by habitual indulgence in opium. All these factors were duly taken into consideration in this study. Moreover, it was found that in nearly half of the cases, alcohol, hemp drugs, arsenic, etc., were being occasionally used by those habituated to opium.

General appearance

It requires an expert eye to detect an opium eater who is taking moderate doses of the drug (up to 10 grains) daily. The majority of these people had a healthy and normal appearance except for the fact that most of them were thinly-built individuals. A small number had dark pigmentation on the face, probably the result of intestinal toxæmia produced by the sluggish action of the bowels and the liver. Out of the entire series, only three individuals had the type of appearance ascribed to opiumad dicts of very old standing—i.e., cachexia,

a pale skin, lack of fat and sallow complexion. These individuals were taking large doses of the drug and at the same time were indulging in other drugs, such as cocaine, morphine or hemp drugs.

Young people taking moderate doses who had not indulged in the habit for a long time appeared to be well nourished, but even they looked flabby. They perspired easily even after slight exertion and were incapable of undergoing any physical or mental strain. Some of them complained of a chilly sensation in the body and had a tendency to shiver on exposure to cold. They stood even slight variations of temperature badly. Individuals addicted to large doses (exceeding 10 grains daily) looked pale and sallow and had a peculiar pigmentation around the mouth, cheeks and eyelids. In such people the eyes were lustreless and sleepy and the conjunctivæ were pale. Many of them suffered from trichiasis, had corneal opacities and suffered from profuse lacrimation. Trichiasis and trachoma are common complaints in the rural areas in parts where opium is taken presumably with the object of ameliorating the troublesome and painful symptoms produced by these conditions. The pupils were contracted in those habituated to taking large doses and reacted to light and accommodation rather sluggishly. The lips were dark and had a bluish tinge.

The effect of opium-eating on the body-weight was studied in about 500 individuals. The average loss of weight in different groups was determined by a comparison with the average weight for the same height and age worked out from the records of various insurance companies. It was established that opium eaters were, as a rule, lighter in weight in comparison with normal individuals. The prolonged use of the drug results in disordered metabolism leading to chronic toxæmia and this probably was responsible for the loss in body-weight.

The prolonged use of opium in infants and children leads to stunted growth. The infants who had been given the drug for prolonged periods were shorter and had deformities of the chest more frequently than other children. They generally had protuberant abdomens.

Effect on Body Organs

Skins. Those habitually indulging in opium often complained of dryness and itching of the skin and even ulcer formation was observed in some. In old *habitués* taking more than 10 grains a day, the skin was dry and lost its usual turgid appearance, natural elasticity and subcutaneous fat. The hair was often dry, lustreless and thin. The dirty habits into which they drifted and the irregularity in taking baths were probably contributory causes. Minor eye troubles such as conjunctivitis and allied conditions were common among them.

Respiration. About 12% of *habitués* examined were found to suffer from minor ailments of the respiratory tract, such as chronic sore throat, coryza, cough, bronchitis and post-nasal catarrh. Habitual use of opium, besides producing general impairment of the body functions, leads to diminished sensitiveness of the mucous membranes of the respiratory tract leading to various respiratory disorders. It undoubtedly delays recovery from various chronic affections of the chest for which the drug is used as a household remedy. Its withdrawal is often followed by the amelioration of the symptoms and sometimes by the cure of these disorders.

Heart and blood vessels. In those taking large doses of opium the pulse is generally small, soft and thready. One who has examined opium addicts can easily make out the typical soft and low tension pulse of a confirmed addict taking large doses. When the habit has persisted for many years the pulse alters its character, becomes full and has high tension; the blood vessels become hard and are not easily compressible.

The majority of the *habitués* who take small doses do not show any signs of anæmia, but those taking large doses look pale and have a sallow colour. The minor degree of anæmia met with among those indulging in large doses of opium can be explained by the fact that the daily income of the majority of these people is just sufficient to meet their daily ordinary requirements. Any extra expenditure on the purchase of opium interferes with their proper nourishment and serves to reduce general vitality. In addition to this the toxic effect of the drug itself after prolonged use is also responsible for these changes. Opium probably does not affect the blood-forming organs directly, but a certain amount of anæmia and deterioration of blood occurs indirectly as a result of the lowering of the general vitality from malnutrition and toxæmia due to constipation.

Digestive tract. The gastro-intestinal tract bears the brunt in those who take opium habitually. In many of these individuals the tongue is dry, flabby, cracked and thickly coated. The breath is offensive, indicating subnormal stomach and liver functions. Most of them suffer from chronic pharyngitis and pyorrhœa and carious teeth are present in a large number. Probably faulty personal hygiene into which addicts allow themselves to drift is responsible to a great extent for these changes. A large number in the series undoubtedly suffered from various disorders of the digestive tract. The common complaints were heaviness over the pit of the stomach probably due to slow emptying of the organ, loss of appetite, constipation alternating with diarrhœa and heaviness in the head commonly occurred in a very large number.

Nausea, although it occurred on withdrawal of the drug, was not seen even in addicts taking large doses. Gnawing pains in the epigastric region was a common complaint. Digestion, especially of carbohydrates, was not interfered with. Opium addicts are particularly fond of sweets and take sugar, molasses, caramel in plenty and digest these well.

In opium addicts activity of the bowels is generally markedly inhibited. In those taking large doses the cæcum and the colon are generally loaded and can be easily felt and rolled under the fingers. The addicts usually spend a long time over defæcation every day. The stools are dry and hard and are ejected in the form of scybalæ and involve considerable straining. A large number of *habitués*, however, stated that they had a regular movement of the bowels every morning before they took their morning dose. Withholding of the drug in some addicts produced symptoms of acute gastro-enteritis, severe pain in the abdomen, followed by diarrhœa and sometimes bloody stools.

Although cirrhosis of the liver produced by intestinal infections and toxæmia is a fairly common occurrence in certain parts of India, no definite relationship with the opium habit was observed. The habitual use of opium does not injure the liver to the same extent as does indulgence in alcohol.

Urinary system. It is commonly believed that opium addicts pass smaller quantities of urine as compared with normal individuals. This was not borne out by observations in this series. There is a common belief among the medical profession that opium causes injury to the kidneys and that persons

suffering from kidney disease stand the drug badly. The effect of opium upon damaged kidneys was studied in a series of cases and it was found that in patients with nephritis moderate doses of up to 5 or 6 grains daily produced no marked effect on the amount of albumin in the urine.

Diabetes. One of the reasons why opium is commonly taken habitually in India is that it is believed to have a curative effect on diabetes. In a series of cases studied from this point of view it was found that opium in doses of 1 to 6 grains daily reduced the total quantity of the urine excreted in mild cases of diabetes. In severe cases, however, it had no effect whatever upon the quantity of urine passed and sugar contained in it. Further, in early and mild cases of diabetes, opium had a well-marked effect in reducing the daily output of the sugar in the urine and in some cases the sugar entirely disappeared. In severe cases no such effect was produced. It is interesting to note that, although opium diminished the amount of sugar in the urine in mild cases of diabetes, it had no effect upon the blood sugar; in fact in severe cases it actually increased the quantity of sugar in the blood. Probably the drug acts by raising the renal threshold for excretion of sugar.

Use of opium as a sex stimulant. There was a widely prevalent belief amongst people in India that opium, when taken in small doses, is an aphrodisiac. This belief had been handed down for generations and may be based on practical experience of the people who have used the drug for ages. It has been asserted that opium is especially useful in sexual impotence in young adults and the drug has been frequently recommended by the practitioners of indigenous medicine in the treatment of sexual neurasthenia, premature ejaculations and spermatorrhœa, due to hyper-excitability of the sexual emotions. It was not uncommon among certain classes of the lower strata of society to take a small dose of opium before the sexual act. It is possible that on account of its general depressant effect on the nervous system, opium may prolong the sexual act and thus prevent premature ejaculation. This may be the reason for the aphrodisiac effects attributed to it.

It may be mentioned here that hemp drugs are also believed to strengthen the sexual act. Perhaps the partial delirium produced by indulgence in these drugs may produce visions of a sexual nature which may result in the stimulation of higher psychical centres. Alcohol may increase the desire for the sexual act by removing the control of the higher centres of the brain on the lower centres. Unlike alcohol, opium prolongs the sexual act without increasing the desire for it. Opium for this reason has been used along with hemp drug and alcohol by dissipated and licentious persons as an aphrodisiac. All these drugs were employed by prostitutes in India as sexual excitants. In females who took opium habitually, irregularity of the menstrual periods was not uncommon. In extreme cases of addiction and with large doses it was found that the habit led to a certain loss of sexual desire and sexual emotions. Some of the males complained of complete absence of sexual desire. Most of them experienced somewhat exaggerated desire after withdrawal of the drug.

Mental and Moral Effects

The mental effects produced by indulgence in opium can be subdivided into temporary effects which are present only when the patient is actually under the influence of the drug and the more permanent effects produced by prolonged habitual use.

Temporary effects. When a person is actually under the influence of opium powerful euphoric effects are experienced: it stimulates and refreshes the individual for a while in every way. It temporarily hides the painful symptoms of any intercurrent disease and it gives a feeling of fitness and well-being. A dose of opium gives rise to pleasurable sensations all over the body, so that the addict is pleased with things round him. He regains his power of concentration of thought and is even inclined to work hard, and take interest in his surroundings and in life generally. The drug also induces forgetfulness of mental worries by depressing the higher centres in the brain.

Habitués when under the influence of a dose displayed buoyancy of spirit and most of them stated that their imaginative powers were stimulated and they could even think more vividly and with clarity. All this is true to a certain extent in the case of persons habituated to small doses who have taken to the drug to relieve worry, fatigue, or minor ailments. These effects are no doubt the result of the dulling of all sensations and reflexes generally.

Permanent effects. While studying the permanent effects of opium addiction on the mental faculties of addicts the following points were kept in view.

(*a*) *Causes which led to habitual use.* In those *habitués* in whom the cause of the habit was disease—e.g., toxæmia due to some infective focus in the gums, teeth, tonsils, etc.—the toxic absorption was in itself sufficient to produce mental depression, irritability and hypersensitiveness. The presenec of such symptoms cannot be attributed to the opium habit but are rather the cause of the development of the habit.

(*b*) *The personality of the addict*—i.e., what sort of individual he had been before he acquired the habit, whether he had been a normal individual with more or less stable nervous system, or with a neuropathic taint. In some cases the habitual use of small doses of opium may help to stabilize a hyper-excitable individual. Habitual criminals sometimes become sedate and settle down to a more or less honest life after taking to the drug.

The popular belief that opium addiction is to be found amongst the degenerates and vicious weaklings does not hold good entirely in the case of Indian addicts. In the large series of cases referred to above, there were quite a large number of good citizens and agriculturists who were working like normal individuals, without any appreciable change in their social behaviour. Many of them took the drug in order to tide over an unpleasant period of their lives, mental worry or strain of excessive work or in some cases bodily pain. These mostly kept to small doses not exceeding 10 grains daily and showed anxiety to get rid of the habit. Among about 500 addicts in whom repeated examinations were carried out at varying intervals for about three years, the majority were found to be normal individuals in whom no apparent mental or moral deterioration could be detected.

The mental faculties are, however, increasingly affected as the dose is increased and, further, the duration of the habit is an important factor. Mental injury is more likely to occur in those taking large doses for prolonged periods. A detailed study of the past history and the personality of this type of *habitué* showed the cause of addiction to be a nervous taint, or a defective personality as a result of which they were led to take this drug. Such persons had a vacant look, sad expressions, their memory was impaired and they were dull and suffered from slow cerebration. Besides, these individuals

showed want of self-reliance, weak will-power, and were often selfish and quarrelsome. Such addicts were found to possess weak morals, showed lack of sense of responsibility, were given to habitual lying and showed well-marked moral depravity. Dosage is an important factor here.

It is a well-known fact that a dose of opium bestows the feelings of euphoria, ease and contentment on account of the loss of sense of responsibility produced by the depression of the higher brain centres and the relaxation of their control over the lower mental faculties. The *habitués* from constant usage of the drug become careless regarding their daily duties and acquire habits of idleness. Addicts of this type usually associate with persons of low morals in order to continue their indolent life. Such a life and the high cost of the drug which they must obtain leads them to depraved habits such as stealing or begging to provide their daily ration. In this way changes in their character are brought about which are partly due to surroundings in which they find themselves but chiefly due to the direct action of the drug which, by acting on the higher brain centres, impairs their power of judgment.

Mental injury. Opium addiction in itself is undoubtedly an important factor in causing mental injury. From a detailed study of the problem, it would appear that in those taking doses of 20 grains and less daily, there were about one-fourth who started the habit to obtain the euphoric effects of the drug, or as a substitute for other drugs, such as alcohol. In those who took over 20 grains, however, nearly half were found to be using the drug on account of its euphoric and sexual effects. This shows that in certain individuals there is an inherent tendency to excesses of all kinds.

Large doses of opium produce greater injury to the central nervous system in those having neuropathic tendencies. A careful study of this aspect shows that this group consisted of care-free pleasure-seeking young individuals mostly of neurotic temperaments with defective personality. In persons possessed of normal stability of mind and body and those who start the habit after the age of 40 years from such causes as fatigue, worry and old age, little or no deterioration of mental faculties could be observed. In none of these individuals could we find any evidence of injury to the nervous system or higher functions of the brain, such as is met with in addiction to alcohol and cocaine.

Relation to society. Opium addicts in this country are not liars or moral wrecks as has been described by some observers. Some of our addicts were upright, straightforward and self-respecting individuals. We have observed that moderate consumers of the drug and a majority of those taking even large doses are generally inoffensive to society. It is only when the excessive use affects the addict physically and morally that he resorts to dishonest practices, but he seldom commits acts of violence. The ordinary types of opium addicts met with in this country are not mentally defective, and the habit does not lead to insanity or serious nervous disorders needing custodial care. They are not dangerous to society, but undoubtedly many of those taking large doses are useless to the community. The opium addicts in India are not much objected to by the people at large, but persons taking large doses of drug, and those who smoke opium are shunned by respectable citizens lest their children and youths should acquire the habit by force of example. The harm done by an opium addict is mainly confined to himself and does not affect society.

The opium habit and crime. Some authorities have remarked that narcotics do not arouse criminal impulses. Whether a person becomes a criminal because of his habit, or an addict because of inherent criminal tendencies, is difficult to determine. Klob (1925), after an intensive study of 255 drug addicts, formed the opinion that the majority were criminals before they became addicts and that no opiate ever directly influenced them to commit a violent crime. It would be hazardous to state that the majority of drug addicts have a low grade of morals and are persons with criminal tendencies, though it is quite true that when an apparently normal person becomes an addict and when he is deprived of his drug, he may do anything to get it. It has been claimed, however, that addiction to opiates does not excite crime unless the drug supply is absolutely cut off or its procuring rendered difficult. Our own experience in India is in accord with these findings. From our intimate contact with opium eaters in this country we are inclined to believe that the opium habit rather inhibits impulses of a violent nature, by lowering the vitality and reducing ambition and courage which prompt a normal individual to abnormal impulses to perform a criminal act. There is thus more possibility of an addict becoming a thief than a murderer. In our series, the nature of the crime in the majority was assistance in smuggling or selling illicit drugs or theft. There were only two persons in this series who had served sentences for more serious offences.

Opium habit and insanity. In the earlier stages of habit-formation, mental brilliancy, lasting as long as the so-called stimulating effects of the drug persist, is observed. Some of the best speeches and a few excellent literary productions are said to owe their inception to opium. Opium does not injure the psychic areas as seriously as alcohol does. The intelligence seems to be spared even in extreme stages, though other functions, such as character, self-control and mental equity are the first to go, and thus render an addict weak-minded and exhausted of energy. In worse cases the memory is weakened and torpor, psychic depression and marked dysthemia intervene. Among the 4,700 cases of insanity collected by Powell (1924) none was due to either eating or smoking of opium. The Police Surgeon and Deputy Commissioner of Police, Bombay, did not report a single case of insanity attributable to opium. Our own observations in the mental hospitals showed that of all the cases admitted only a few gave the history of opium habit. Evans (1904) in his paper on insanity in India, showed that 20% of insanity is due to hemp drugs and has cited no case at all in which insanity could be attributed directly to opium. He writes, "It is my deliberate opinion that opium never directly causes insanity. Even if an insane person has been found to be an addict, it is quite possible that there may be some hereditary tendency towards congenital psychopathy and psychic disturbances of hysteric nature and mental weakness to account for it."

Our own work in the mental hospitals at Ranchi, Agra, Lahore, Benares, Poona and Thana corroborates this view. Among our series of 1,070 opium addicts we had only three cases of insanity. Although no family history of insanity could be elicited, all these three persons were, in addition, addicted to hemp drugs in the form of *bhang* and, therefore, opium could not be held entirely responsible for the condition. It may, however, be at the most an exciting cause along with hemp.

Opium habit and fecundity. The case histories of a large number of addicts were carefully investigated, but there

are difficulties in getting dependable information. The finding of the gross or net number of children in the whole series serves no useful purpose as about 50% of the *habitués* start taking opium when their sexual powers are on the decline and their fecundity normally exhausted or at low ebb. However, the histories of 500 cases who were either taking opium at the time of marriage or had started it within two years of their marriage and who had been taking the drug for over 15 years, were carefully investigated. It was found that the average number of children per 100 families was 273.2, whereas according to the normal fertility curves this figure worked out to 375.39 children per 100 families. The 1931 census gave the figure as 396 per 100 families for all castes and ages in India. We were therefore justified in concluding that the fecundity in our series was appreciably lower as compared to the general population.

Further, according to the census figures of 1931, only 1% of all marriages were sterile, whereas in our series 86 marriages or 17.2% were sterile. The higher rate of sterility amongst opium addicts may of course not be entirely due to the direct effect of the drug, but may in considerable measure be due to neglect of the wife on the part of the husband, venereal disease, psycho-neurosis and sexual neurasthenia and such other factors as are sequelæ to the drug habit.

SELECTED REFERENCES

Govt. of India	1893-94	*Report of the Royal Commission on Opium.*
Sceleth & Kuh.	1924	Drug Addiction. *Jour. Amer. Med. Assn., LXXXII,* No. 9.
Gavit, J. P.	1925	*Opium*
Chopra, R. N. & Grewal, K. S.	1927	Opium Habit in India. *Ind. Jour, Med. Res., XV,* No. 1.
Chopra, R. N.	1928	The Present Position of the Opium Habit in India. *Ind. Jour. Med. Res., XVI,* No. 2, Oct.
Chopra, R. N., Grewal, K. S., Chowhan, J. S. & Chopra, G. S.	1930	Addiction to " Post " (unlanced capsules of Papaver somniferum) in India. *Ind. Jour. Med. Res., XVII,* p. 389.
Chopra, R. N., Mukherjee, D. & Dikshit, B. B.	1930	Narcotine. Its Pharmacological Action and Therapeutic Uses. *Ind. Jour. Med. Res., XVIII,* p. 35.
Chopra, R. N. & Knowles, R.	1930	The Action of Opium and Narcotine in Malaria. *Ind. Jour. Med. Res., XVIII,* p. 5.
Chopra, R. N. & Chopra, G. S.	1931	Opium and Albuminuria. *Ind. Med. Gaz., LXVI,* p. 299.
Chopra, R. N. & Ghosh, N. N.	1931	Addiction to " Post " (unlanced capsules of Papaver somniferum), Part II. *Ind. Jour. Med. Res., XIX,* p. 415.
Chopra, R. N. & Bose, J. P.	1931	Psychological Aspects of Opium Addiction. *Ind. Med. Gaz., LXVI,* p. 663.
Chopra, R. N., Bose, J. P. & De, N. N.	1931	Further Observations on the Effect of Opium on Blood Sugar. *Ind. Med. Gaz., LXVI,* No. 11, Nov.
Chopra, R. N. & Bose, J. P.	1931	Effect of Opium on the Blood-sugar of Non-diabetics. *Ind. Jour. Med. Res., XVIII,* No. 4, April.
Chopra, R. N., Chopra, G. S. & Grewal, K. S.	1932	The Opium Habit in the Punjab, Part I. *Ind. Jour. Med. Res., XX,* p. 545.
Chopra, R. N. & Chopra, G. S.	1934	Administration of Opium to Infants in India. *Ind. Med. Gaz., LXIX,* No. 9.
Chopra, R. N. & Chopra, G. S.	1935	Opium Habit in India. Studies on the Physical and Mental Effect produced by Opium Addiction. *Ind. Jour. Med. Res., XXIII,* No. 2, Oct.
Chopra, R. N. & Chopra, G. S.	1927	The Treatment of Opium Habit with Lecithin and Glucose. *Ind. Med. Gaz., LXXII,* No. 5.
Chopra, R. N. & Chopra, G. S.	1938	The Opium-smoking Habit in India—Present Position, Parts I, II, III. *Ind. Med. Gaz. LXXIII,* No. 2, 3 & 4.
Chopra, R. N. & Roy, A. C.	1937	Observations on the Blood-Lipoid Changes in Opium Addicts. *Ind. Jour. Med. Res., XXV,* No. 1, p. 105.
Chopra, R. N. & Ganguli, S. C.	1939	Abstinence Symptoms of Opium Addiction and the Role of Glucose in Their Treatment. *Ind. Jour. Med. Res., XXVI,* No. 3, Jan.
Chopra, R. N. & Chopra, G. S.	1940	Withdrawal Syndrome in Opium Addicts and the Rationale of Treatment with Lecithin and Glucose. *Ind. Jour. Med. Res., XXVIII,* No. 1, July, pp. 225-233.
Chopra, R. N. & Chopra, G. S.	1940	Treatment of Opium Addiction with Lecithin and Glucose and Its Effects on Abstinence Symptoms. *Ind. Med. Gaz., LXXV,* No. 7, July.
Chopra, R. N. & Roy, A. C.	1941	Urinary Excretion of Morphine in Opium Addicts with and without Lecithin Glucose Treatment. *Ind. Jour. Med. Res., XXIX,* No. 1, January, pp. 192-201.
Govt. of India, Central Board of Revenue	1949	*An Historical Note on the Evolution of the Opium Policy, Internal and External, of the Government of India.*

TECHNICAL

Fate of Morphine, Diacetylmorphine and Codeine in the Human or Animal Body

By Harry Peterson
New York State Racing Commission Laboratory

An accurate knowledge of the transformations of a drug that occur after its ingestion may determine whether it can be chemically detected or not in the body after death or in the excretions or secretions of the living body. It may appear unchanged or as entirely different substances, and the methods of analysis employed must be modified accordingly.

Narcotics constitute a group of drugs of interest both to racing chemists and to toxicologists. Before coming to a discussion of the particular narcotics named in the title of this paper, the general reactions of drugs in the body may be considered.

Chemical Reactions Occurring in the Body

Reactions which can take place in the body include oxidation, reduction, hydrolysis, and a number of synthetic reactions or conjugation processes. R. Tecwyn Williams, in his book *Detoxication Mechanisms* (1), lists nine such synthetic reactions, five of which have been reported to occur with the drugs of most interest to racing chemists. They are:

1. Glucuronic acid conjugation
2. Ethereal sulfate conjugation
3. Glycine conjugation
4. Acetylation
5. Methylation

Detoxication may involve only one of these reactions, or several may take place successively or concomitantly, depending on the structure of the substance ingested. In the subsequent discussion, most of the material has been taken from Williams (1). Other sources of information are noted as they occur.

Hydrolysis

This reaction occurs with esters like atropine, cocaine, and procaine. The de-acetylation of diacetylmorphine likewise is hydrolytic. In every case the presence of enzymes is important.

Oxidation

Oxidation occurs in a number of ways and is largely dependent on the structure of the compound. Amines, notably many sympathomimetic amines, are oxidized in the body, with enzymes like amine catalysing the reactions. Methyl groups may be removed by oxidation also. In radioactive-tracer experiments with rats given codeine, in which the methoxyl group is labelled with carbon 14, $C^{14}O_2$ is found in the expired air. Primary alcohols are oxidized to the corresponding acids.

Reduction

Reduction of foreign substances in the body appears to be less common, but a well-known example of a reduction process after the administration of a drug is the reduction of chloral hydrate *in vivo* to trichloroethyl alcohol. This is usually followed by combination with glucuronic acid to form the trichloroethylglucuronide, urochloralic acid.

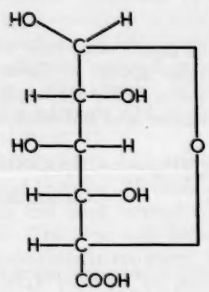
$$CCl_3CHO + 2H \longrightarrow CCl_3CH_2OH$$

Glucuronic Acid
conjugation

$$CCl_3CH_2OH \longrightarrow CCl_3CH_2OC_6H_9O_6$$

Synthetic reactions

1. Glucuronides



Glucuronic Acid

The formation of conjugates with glucuronic acid is probably the most common synthetic process in the body. Two kinds of such glucuronides are known. One is an ether type which is formed by reaction with hydroxyl groups in almost any type of compound except carbohydrates. The other is an ester type formed by reaction with carboxyl groups attached to aromatic nuclei. The ether type is usually stable in alkali and does not reduce alkaline copper reagents, whereas the ester glucuronides are unstable in alkali, and the glucuronic acid liberated reduces such reagents. In the case of urochloralic acid, however, its ability to reduce Fehling's solution is attributed to the instability in the presence of strong alkali of three halogen atoms attached to the same carbon.

The morphine molecule contains both a phenolic and an alcoholic hydroxyl group. In codeine the phenolic hydroxyl is methylated, and only the alcoholic one is available for conjugation. Glucuronides are formed with both compounds (2). Morphine, however, is capable of still another

reaction which results in the formation of ethereal sulfates, found together with glucuronides in the urine after morphine ingestion.

2. Ethereal Sulfates

These are formed only by combination with phenolic hydroxyl groups, the product being an aryl sulfuric acid, $R\text{-}OSO_3H$. This reaction accounts for a considerable portion of the combined morphine excreted by dogs (1). Epinephrine not oxidized in the tissues is excreted as a sulfuric ester, which may be epinephrine-(3 or 4)-hydrogen sulfate. Phenylethylamine and most other amines are oxidized by amine oxidases, but in the case of epinephrine conjugation is more rapid than oxidation and is therefore the dominant reaction (1).

3. Glycine Conjugates

The formation of hippuric acid from benzoic acid in the organism is the best-known example of this reaction, which consists of the combination of glycine with an aromatic acid to form an aroyl glycine. The reaction takes place with carboxyl groups attached to the nuclei of benzene, naphthalene, thiophene, furane, and pyridine, the carboxyl group of the phenylacetic acids, and carboxyl groups separated from the aromatic nuclei by vinyl groups. In this class is the conversion of nicotinic acid and nicotinamide to nicotinuric acid, $C_5H_4NCONHCH_2COOH$, which, in the horse, is the main excretion product of nicotinic acid. This is of special interest because nicotinamide is a metabolite of nikethamide (3, 4).

4. Acetylation

Acetylation in the body occurs only with aromatic amino groups and the amino groups of alpha amino acids. The amino groups of sulfonamides are largely acetylated, as are those of p-aminobenzoic acid and esters like procaine.

$$NH_2C_6H_4SO_2NH_2 \longrightarrow CH_3CONHC_6H_4SO_2NH_2$$

Sulfanilamide — p-Acetaminosulfanilamide

5. Methylation

Although probably a common reaction in the organism, methylation, from the viewpoint of detoxication mechanisms, is confined to the heterocyclic nitrogen of the pyridine and quinoline rings. In man nicotinamide is methylated to N^1-methylnicotinamide and excreted as such (5). Large doses of nicotinamide also result in the excretion of nicotinuric acid, as in the horse (6).

Drug Metabolism Variations among Different Animal Species

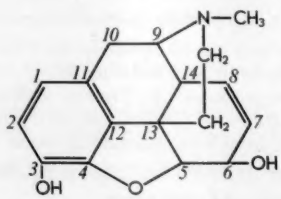
Considerable specific information is available about the fate of many drugs after administration to laboratory animals such as the dog, guinea-pig, rat and rabbit. Much is known about drug metabolism in man, of course, because most pharmacological research is designed to secure information that can be applied in human medicine.

The absorption of drugs by the ruminant and the simple-stomached animal is not the same. Further, in the latter group carnivora and herbivora show differences, whereas omnivorous animals may show similarities to both. Absorption in the short digestive tract of the dog is relatively more efficient than in the longer digestive tract of the horse, which is adapted to forage and grains. In the case of ruminants certain drugs may be destroyed in the rumen or may be so mixed with indigestible fibre as to pass through the rumen digestive tract largely unabsorbed. The presence of enzymes in certain species and their absence in others account for variations between species. For instance, because of the presence of atropinase in the liver of the rabbit, atrophine is decomposed more readily than in other animals, notably swine (7). Procaine is almost completely hydrolysed in man, but in the horse hydrolysis is much less complete (8). In man, the rat, and the guinea-pig, N^1-methylnicotinamide is an important metabolite of nicotinic acid. It does not appear in the horse, rabbit, and sheep (1, 9).

Bearing in mind that such differences exist, examination of existing data does, nevertheless, show that animals belonging to the herbivorous group metabolize drugs similarly, and the same is true for carnivorous and omnivorous animals. Further, there are general similarities among all three classes which permit limited analogies to be drawn when data on certain species only are available. Information has been collected about the fate of drugs in all species that have been studied, and will be given in detail under each drug as the data are presented.

Morphine

Relation of Chemical Structure to Metabolism

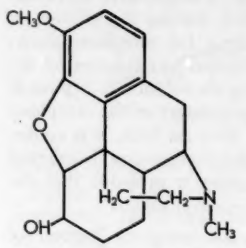


This important drug has been investigated by many workers, but definite information about the metabolic changes which take place after its ingestion has been forthcoming only within relatively recent years. It is a phenanthrene derivative with two additional heterocyclic rings, one of which includes the tertiary amine nitrogen that gives the substance its basic properties. Its structure likewise includes one secondary, alcoholic hydroxyl group (position 6) and the phenolic hydroxyl group (position 3).

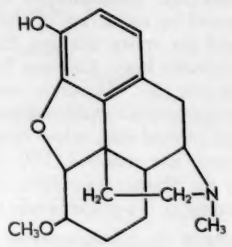
Oxidation at the nitrogen atom with removal of the methyl group has been demonstrated by the administration of morphine having carbon 14 in the methyl group attached to the nitrogen to both rats (10) and human subjects (11). In both, $C^{14}O_2$ was detected in the expired air.

Both hydroxyl groups may undergo conjugation. Oberst (2) investigated the urinary excretion in morphine addicts of the following derivatives of morphine: 3,6-diacetylmorphine (heroin), alpha-isomorphine, 3-methylmorphine (codeine), dihydroheterocodeine, dihydrocodeine, dihydroisocodeine and dihydrocodeine methyl ether. The amounts of these substances, both free (unconjugated) and bound (conjugated), found in the urine after administration were determined and compared with similar results for morphine itself. Morphine, alpha-isomorphine, 3-methylmorphine, and dihydroheterocodeine were excreted in both free and bound forms. The bound fraction was two to ten times greater than the free in every instance. 3,6-diacetylmorphine (heroin) was excreted as morphine in both forms. Dihydrocodeine and dihydro-

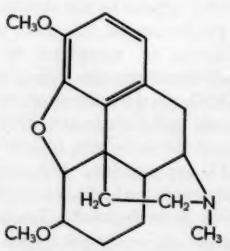
isocodeine were excreted mainly in the free form, only small amounts being bound. Dihydrocodeine methyl ether was excreted only in the bound form. Thus, conjugation occurred only when either one or none of the hydroxyl groups was methylated. No conjugation occurred when both were methylated. Differences were noted between the stereoisomers, morphine and alpha-isomorphine and dihydrocodeine and dihydroisocodeine, giving rise to the speculation that molecular spatial arrangement affects the conjugation. No reason was apparent for the conjugating reaction being diminished in the hydrogenated codeine compounds. The 3,6-diacetylmorphine was apparently first diacetylated and then metabolized as morphine. No evidence was found that a methyl group on either the phenolic or alcoholic hydroxyl group was altered or split off by the body.



Dihydrocodeine



Dihydroheterocodeine



Dihydrocodeine methyl ether

N-allylnormorphine, which differs from morphine only in the alkyl group attached to the nitrogen, is conjugated by surviving liver slices at the same rate as is morphine (12).

Absorption of Morphine

Morphine is rapidly absorbed from all mucous surfaces. It is readily absorbed from the small intestine, and some may be absorbed from the stomach. It is absorbed promptly following subcutaneous injection. It is not absorbed through the intact skin, but a scarified epithelium permits slow entrance to the circulation (7). It passes from the blood into the tissues, where it is temporarily stored (13).

Dog

A dog begins to eliminate morphine in the urine and fæces immediately after absorption (7). Much of the early work on the elimination of morphine after administration to dogs and other animals was subject to uncertainties inherent in the analytical methods employed (13, 14). The proportions of the drug excreted in the urine and the fæces were uncertain, and widely-varying results were reported by many workers. Nevertheless, the drug was found in both excretions consistently. Using improved methods, Wolff, Riegel, and Fry (14) found that at any level of single or repeated doses of morphine between 2 and 200 mg. normal dogs excreted, on the average, 20% of the drug. Two-thirds of the excreted morphine was recoverable in the urine and one-third in the fæces. None was found in saliva. Liaci (15) reported that 3.92% to 5.61% of morphine injected hypodermically into dogs was eliminated in the fæces. According to Inoue (16) a ten-milligramme quantity of morphine hydrochloride incubated with a ten-gramme portion of dog-liver slices can be recovered to the extent of 52% to 82%.

Gross and Thompson (17, 18) showed that morphine was excreted in " free " and " combined " forms by both habituated and non-habituated dogs. Using suitable hydrolysis methods, total recoveries from non-tolerant dogs of 80% to 92% of the amount administered were obtained. From habituated dogs 35% to 66% was recovered. The " combined morphine " in the urine of dogs treated with morphine could be separated into easily and difficultly hydrolysable portions. Tolerant dogs excreted relatively greater amounts of the easily hydrolysable fraction, and non-tolerant dogs excreted much more of the difficultly hydrolysable fraction. Liver damage induced by carbon tetrachloride affected the conjugation of injected morphine (19). The total morphine recoverable in the urine was not changed, but the easily hydrolysable fraction of conjugated morphine was decreased, and free morphine was proportionately increased.

The exact nature of the conjugated forms of morphine excreted by the dog is uncertain. According to Williams (1) the work of Stolnikow in 1884 indicated that in dogs the drug formed an ethereal sulfate. Gross and Thompson (17) reported that the easily hydrolysable form is hydrolysed at pH 1 in 60 minutes at a temperature of 100° C. and accounts for 30% of the combined morphine excreted by non-tolerated dogs. It is apparently not a glucuronide. It may be an ethereal sulphate in which the sulphuric acid group is attached to the phenolic 3-hydroxyl group (1).

The following results seem to disagree with these suggestions. Seibert, Williams and Huggins (20) made a study of the urine from a dog which had been infused with 4 grammes of morphine sulphate. The free and bound morphine were separated chromatographically on paper with butyl alcohol-acetic acid-water after removal of urea with urease and concentration. Munier's alkaloid spray yielded two spots, one corresponding to morphine. The other was extracted with methanol and distilled water, the residue recrystallized, hydrolysed with betaglucuronidase and chromatographed on paper. The chromatogram indicated the presence of morphine, glucuronolactone, and glucuronic acid. An additional unknown spot was observed.

Morphine sulfuric ether given parenterally to tolerant and non-tolerant dogs is excreted in the urine as both free and bound morphine, but in lower amounts than reported for morphine itself (21).

Woods (22, 23) reports that the distribution of free and bound morphine in dogs and rats after administration of the drug is selective for certain tissues and fluids. Free morphine predominates in spleen, pancreas, thyroid, and adrenal tissues, but in lung, liver and kidney both free and bound forms are found. Very much higher concentrations are found in bile from the gall bladder than elsewhere. Brain, cerebrospinal fluid, and fat contain very little in either form. Biliary morphine is the principal source of fæcal morphine.

Bound morphine from the bile is only a partial source of the morphine excreted in the urine in the first 24 hours after administration, but it is probably the source of all the bound morphine that is excreted in the urine after 24 hours. One abundant form of bound morphine in dog urine can be identified, after separation by chromatography, as the phenolic group-substituted monoglucuronide. Another form of bound morphine appears to be a different glucuronide of uncertain composition.

Man

Much of the work on the metabolism of morphine in humans has been done in connexion with studies of subjects addicted to the drug. In these an approximate average of 30% (11% to 55%) of varying doses of injected morphine is excreted in the urine, 5% free and 25% conjugated (24, 2). The remaining 70% is unaccounted for. It may be oxidized or eliminated as unidentified degradation products. That morphine is excreted as a conjugate with glucuronic acid is evident because the glucuronic acid output rises in proportion to the dose (2). Conjugation can occur at either the 3- or 6-hydroxyl group (2), but the exact nature of the glucuronide formed has not been determined. When the administration is oral, the amount excreted in the free state is less and the amount excreted combined is greater than when the administration is parenteral. Morphine is excreted in the urine of opium addicts (25, 26), and is found both " free " and " bound " in the urine of morphine addicts (24, 27). The fæces, liver, and perspiration of human addicts contain free morphine, bile contains only conjugated morphine, and urine and gastric contents contain both free and conjugated morphine. No morphine was found in saliva and blood (27).

In a case of lethal poisoning from the subcutaneous administration of morphine the drug was found only in the urine (5 mg./100 ml. before hydrolysis and 17.7 mg./100 ml. after hydrolysis). None was found in the liver, blood, stomach contents, and intestines. None could be found in the liver even after strong hydrolysis (28).

According to Autenreith (29) morphine is only slightly decomposed in cadavers even during putrefaction lasting for a long time. In the stomach and contents of an adult who took 25 grammes of tincture of opium and died four hours later, he found 0.028 gramme of nearly pure morphine. The drug was also found in the urine.

Morphine sulphuric ether given parenterally to addicts, non-addicts, and post-addicts is excreted as both free and bound morphine (21).

More recent studies have been made with non-addicts of the excretion of carbon 14 (from the N-methyl group) after administration of single therapeutic doses of labelled morphine (11). The major portion of the radioactivity is excreted in 24 hours. Urinary excretion accounts for most of the recovered activity, and fæcal excretion accounts for 7% to 10% of the doses (intestinal excretion apparently being less important in man than in the rat). Pulmonary excretion of $C^{14}O_2$ ranges from 3½% to 6% of the injected dose in 24 hours.

Traces of morphine can usually be found in saliva and sweat after administration (29, 30, 31). According to Munch (32) and Sollmann (13) Rosenthal appears to have been the first to demonstrate that morphine is eliminated in the saliva. It was consistently found in the saliva of hospital patients who were given therapeutic doses. Amounts ranged from 0.05 to 0.2 mg. of morphine.

Rat

Rats excrete the greater part of a dose of morphine in conjugated form (33). In those which have developed tolerance the amount of conjugated morphine in the urine is decreased, but the free morphine remains the same. Liver slices from morphine-tolerant rats conjugate more morphine than liver slices from non-tolerant rats. The amount conjugated by liver sections from either is from 37% to 50% of morphine added (34). No oxydimorphine is found in the tissues of either normal or habituated rats after administration of the drug (34). The development of tolerance is not due to metabolism of the morphine in the liver, spleen, or gastro-intestinal tract (35). Incubation of morphine with rat-liver slices followed by extraction of the material, boiling the solution in acid for thirty minutes, and analysis for morphine shows a sizeable loss. This was first attributed to oxidation by the rat liver (36). However, autoclaving the solution at 20 pounds gauge pressure enabled quantitative recovery of the morphine and proved that, when incubated with rat liver, it is conjugated, not oxidized (37). Also, the conjugation is effected in the absence of sulfate ion, making it probable that the conjugate is a glucuronide, not an ethereal sulfate.

After the administration of labelled morphine (carbon 14 in the N-methyl group) (10) to rats, the greatest concentration of radioactivity occurs in the urinary and intestinal tracts. Only minimal amounts appear in the central nervous system. Urinary excretion predominates, but there is evidence of an enterohepatic circulation of morphine or its metabolites following initial excretion into the bile. Male rats excrete significantly more $C^{14}O_2$ via the pulmonary route than females. Liver slices from male and female rats liberate $C^{14}O_2$ from labelled morphine, and the recoveries follow the same pattern as those for the *in-vivo* experiments. It is suggested that some morphine is probably converted to normorphine, which may be excreted either free or conjugated. Similar demethylation has been observed with codeine (38) and with meperidine (39). Tolerant animals do not demethylate more morphine than normal animals.

Rabbit

Normal rabbits after single subcutaneous injections of 50 to 200 mg./kg. of morphine hydrochloride eliminate more in the urine than in the fæces. Elimination is nearly complete within two days, and the total excretion ranges from 7% to 11%, the remainder being destroyed in the organism (40). Liver slices conjugate morphine (37). A ten-milligramme quantity of morphine hydrochloride incubated with a 10-gramme portion of rabbit liver slices is recovered to the extent of 48% to 51% (16).

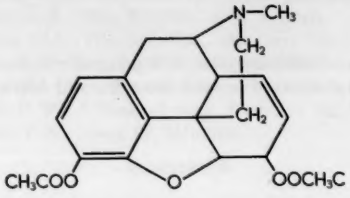
Horse

In experimental administrations of morphine to horses, both oral and parenteral, the drug has been detected in both saliva and urine (41, 42, 43, 44, 45). It is frequently found in saliva after parenteral administration (42). This indicates that actual excretion of the drug in the saliva does take place. The appearance of it in saliva after oral administration can conceivably be attributed to retention of some of the drug in the mouth, which is not possible, of course, when it is given parenterally.

Other Species

Normal cats after a single subcutaneous dose of 50 mg./kg. eliminate 11% to 27%, mostly in the urine. Normal hens after a single subcutaneous dose of 100-200 mg./kg. eliminate 10% to 13% (40).

Ten-milligramme quantities of morphine hydrochloride incubated with 10-gramme portions of liver slices from various animals at room temperature for thirty minutes can be recovered in the following percentages: cat, 50 to 74; guinea pig, 48 to 57; pigeon, 43 to 60; hen, 41 to 58 (16).



Diacetylmorphine (Heroin)

Relation of Structure to Metabolism

Heroin (3,6-diacetylmorphine) is readily hydrolysed to morphine. In alkaline solution (0.5 M Na_2CO_3 at 26°C.) about 58% is hydrolysed in 2 minutes and 88% in 10 minutes (46). Metabolism in the animal body involves, first, hydrolisis and, second, metabolism of the morphine produced by the hydrolysis.

Rabbit

Rabbit serum de-acetylates heroin. However, differences in the extent of the hydrolysis by individual animals have been demonstrated. In experiments using the sera from six male albino rabbits, Wright (47) observed that the sera of three of them liberated acetic acid (measured by the liberation of CO_2 from sodium bicarbonate) corresponding to 85% of the theoretical amount for hydrolysis of both acetyl groups. Sera from the other three animals hydrolysed the heroin more slowly and liberated acetic acid corresponding to 85% of the theoretical amount for only one acetyl group. Repeated observations confirmed these results. 6-monoacetylmorphine was then subjected to action by the rabbit sera, and it was found that the sera which could hydrolyse both acetyl groups of heroin were also able to hydrolyse the 6-acetyl group of the 6-monoacetylmorphine. Sera from the other three rabbits were not. Therefore, the serum from each of the rabbits was able to remove the 3-acetyl group of heroin, but that of only three could remove both groups. Sera from each of the six rabbits liberated acetic acid from diacetyldihydromorphine equivalent to 100% of the theoretical amount for one acetyl group. The sera from the three rabbits unable to de-acetylate 6-monoacetylmorphine hydrolysed diacetyldihydromorphine at a much slower rate. No serum was found which was able to remove the 6-acetyl group from the latter compound (48).

The tissue found to have greatest enzyme activity was liver, followed in approximate order by kidney, brain, blood serum, and muscle. There was some evidence that the enzyme which catalyses the hydrolysis of atropine also catalyses the hydrolysis of heroin in the 6-position. There was also evidence that cholinesterase was not involved in the de-acetylation of heroin at either the 3- or 6-position (49).

Ellis (50) found that the activities of rabbit plasma and liver were due to three distinct esterases. The monoacetylmorphine esterase, specific for the 6-acetyl group, was also found in the sera of man, dog, sheep, and guinea-pig. It was not present in the corpuscles. Most sera hydrolysed the 3-acetyl group of heroin, and the hydrolysis of this group appeared to be a function of the tributyrinase but not of the enzymes that hydrolyse methyl butyrate, acetylcholine, or acetylsalicylic acid.

Man

Human sera and tissues contain enzymes which de-acetylate heroin and dihydroheroin (diacetyldihydromorphine) (47, 48, 49). The rate of de-acetylation for human serum is distinctly slower than for rabbit serum (47), but in the body heroin seems to be completely hydrolysed (46). In addicts physical dependence on morphine is satisfied by heroin, and the ratio of physical-dependence-satisfying doses of morphine sulfate and heroin hydrochloride is 2 : 1. About 7% of either drug is excreted in the urine as free morphine and about 50% as conjugated morphine.

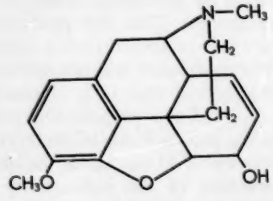
Horse

Heroin is decomposed by horse serum. It is assumed that an esterase is the active agent and that one or two moles of acetic acid are formed (51).

Heroin can be detected in saliva (as morphine) after administration to horses. This was proved in early experiments designed to establish the value of saliva as a medium for the detection of doping (52). This author did not give details of the identifying tests, but it may be assumed that morphine, not heroin itself, was the substance actually present. The drug can be detected (as morphine) in both saliva and urine from horses after oral administration of 2.5 to 3 grains of heroin hydrochloride and after parenteral administration of 0.5 to 0.75 grains (42). Samples of blood taken after two parenteral administrations proved to be negative.

Other Species

Sera and tissues from dogs, guinea-pigs, rats, and sheep have been shown to hydrolyse heroin (50). The degree of activity varies from species to species (49).



Codeine

Relation of Structure to Metabolism

Codeine (3-methylmorphine) has only the 6-hydroxyl group available for conjugation. Such conjugation has been shown to occur in man (2). Demethylation of the 3-methoxy group with the formation of morphine has been demonstrated (53, 54, 55), as well as demethylation of the N-methyl group with the formation of norcodeine (38).

Man

Oberst (2) found that the urinary excretion of codeine in morphine addicts after substitution (24) for morphine amounted to 11.2% of the dose in the free form and 31.6% in the conjugated form. The total amount excreted was slightly greater than that for morphine. Unaltered codeine conjugate was not extractable with an organic solvent. The free drug could be removed from the urine of an addict, the remaining urine subjected to acid hydrolysis and codeine detected in the hydrolysate.

Sollmann (13) states that codeine is excreted as such in the urine without demethylation. There is, however, more recent evidence that it is demethylated to morphine in man, free morphine being isolated from the urine of human subjects given 130 mg. of codeine orally in divided doses (55). After an oral administration of codeine phosphate in man, there was found a considerable quantity of an unknown metabolite, in addition to previously observed metabolites—that is, morphine and conjugated codeine base (54). When subjected to counter-current distribution studies, this substance proved to have characteristics identical with those of N-demethylated codeine (norcodeine). Only part of the norcodeine excreted appeared in the free form, hydrolisis under 20 pounds pressure being required to recover the remainder (38).

Dog

Dogs are reported to excrete about 80% of administered codeine, mainly in the urine but some in the fæces. Repeated administration does not increase its destruction (13).

Sanfilippo (56, 57, 58) found that injections of 0.15 to 0.5 mg./kg. of morphine produced hyperglycæmia in dogs. Daily injections of 5 mg./kg. of codeine for one week caused habituation, so that 0.5 mg./kg. of morphine no longer caused hyperglycæmia. This was considered evidence that codeine is demethylated *in vivo* by the dog.

Rat

Demethylation by the rat, *in vivo* and *in vitro*, of codeine labelled with $C^{14}H_3$ at the 3-position has been demonstrated (53). The methyl group is oxidized and eliminated as $C^{14}O_2$. The *in vitro* studies showed that the liver was the most important site for the demethylation. Comparison of residual codeine results by the methyl orange technique (59) with results obtained by measuring carbon 14 radioactivity showed good agreement. Thus the production of $C^{14}O_2$ was probably the result of demethylation rather than transmethylation. Demethoxylation was not definitely ruled out, but Bernheim (36) showed that 13% of codeine incubated with liver slices appeared as a phenolic-OH compound, and it is probable that the process is one of demethylation. After a subcutaneous injection of 40 mg./kg. of the labelled codeine, approximately one-fifth of the radioactivity appeared as $C^{14}O_2$ in the expired air within 2 hours, 40% within 6 hours. Latham and Elliot (60) reported $C^{14}O_2$ in the expired air of rats administered carbon 14-methoxy-labelled codeine. Codeine was excreted unchanged by the kidney and also into the lumen of the gastro-intestinal tract. The liver was found to metabolize the labelled codeine to a substance with solubility characteristics different from those of codeine itself. This unidentified radioactive substance was excreted into the duodenum via the biliary tract. The liberation of morphine from codeine by incubation with rat-liver slices was demonstrated by Adler and Shaw (54). The total amount of morphine formed represented less than half of the metabolized codeine, and the liberated morphine was further metabolized by conjugation. Identification of the morphine was effected by means of the ultraviolet spectrum of the recovered metabolite, preparation of the 2,4-dinitrophenyl derivative, and comparison of its crystal form, ultraviolet spectrum, and X-ray diffraction pattern with those of the known morphine derivative. After subcutaneous injection of codeine labelled with carbon 14 in the N-methyl group (4 mg./kg.) about 13% of the amount given appeared as $C^{14}O_2$ in the expired air (45).

Horse

After an oral administration of 30 grains of codeine phosphate the drug was detected in both the urine and saliva (45).

References

1. Williams, R. T. : *Detoxication Mechanisms*, Wiley (1947).
2. Oberst, F. W. : *J. Pharmacol. Exptl. Therap.*, *69*, 240 (1940).
3. Ellinger, P.; Abdel Kader, M. M. : *Biochem. J.*, *44*, 77 (1949).
4. Coulson, R. A.; Steward, C. A. : *Proc. Soc. Exptl. Biol. Med.*, *61*, 364 (1946).
5. Huff, J. W.; Perlzweig, W. A. : *J. Biol. Chem.*, *150*, 394 (1943).
6. Johnson, B. C.; Hamilton, T. S.; Mitchell, H. H. : *ibid.*, *159*, 231 (1945).
7. Jones, L. M. : *Veterinary Pharmacology and Therapeutics*, Iowa State College Press (1954).
8. Brodie, B. B. : *Bulletin No. 80*, Association of Official Racing Chemists (1949).
9. Johnson, B. C.; Lin, Pei-Hsing : *J. Am. Chem. Soc.*, *75*, 2971 (1953).
10. March, C. H.; Elliot, H. W. : *Proc. Soc. Exptl. Biol. Med.*, *86*, 494 (1954).
11. Elliot, H. W.; Tolbert, B. M.; Adler, T. K.; Anderson, H. H. : *ibid.*, *85*, 77 (1954).
12. Seibert, R. A.; Huggins, R. A. : *ibid.*, *82*, 518 (1953).
13. Sollmann, T. : *Manual of Pharmacology*, 6th Ed., Saunders.
14. Wolff, W. A.; Riegel, C.; Fryse, E. : *J. Pharmacol. Exptl. Therap.*, *4*, 391 (1933).
15. Liaci, L. : *Arch. Farmacol. Sper.*, *72*, 38 (1941).
16. Inoue, T. : *Japan J. Med. Sci. IV, Pharmacol.*, *12*, No. 283; *Proc. Japan. Pharmacol. Soc.*, *13*, 75 (1940).
17. Gross, E. G.; Thompson, V. : *J. Pharmacol. Exptl. Therap.*, *68*, 413 (1940).
18. Gross, E. G.; Thompson, V.: *ibid.*, *72*, 138 (1941).
19. Gross, E. G. : *Proc. Soc. Exptl. Biol. Med.*, *51*, 61 (1942).
20. Seibert, R. A.; Williams, C. E.; Huggins, R. A. : *Science*, *120*, 222 (1954).
21. Oberst, F. W. : *J. Pharmacol. Exptl. Therap.*, *80*, 188 (1944).
22. Cochin, J.; Haggart, J.; Woods, L. A.; Seevers, M. H. : *ibid.*, *111*, 74 (1954).
23. Woods, L. A. : *ibid.*, *112*, 158 (1954).
24. Oberst, F. W. : *ibid.*, *69*, 240 (1940).
25. Chopra, R. N.; Chopra, G. S.; Roy, A. C. : *Indian J. Med. Research*, *29*, 195 (1941).
26. Liang, C. K. : *Natl. Med. J. China*, *22*, 507 (1936).
27. Oberst, F. W. : *J. Pharmacol. Exptl. Therap.*, *74*, 37 (1942).
28. Zwikker, J. J. L.; Steenhauer, A. J. : *Pharm. Weekblad*, *79*, 241 (1952).
29. Autenreith, W. : *Laboratory Manual for Detection of Poisons and Powerful Drugs*, Tr. Warren, W. H., 6th Ed., Blakiston (1928).
30. Krueger, H.; Eddy, N. B.; Sumwalt, M. : *U.S. Public Health Service, Suppl.* No. *165*, 1 (1941); 813 (1943).
31. Milks, H. J. : *Veterinary Pharmacology, Materia Medica and Therapeutics*, 6th Ed., Eger (1949).
32. Munch, J. C. : *J. Am. Pharm. Assoc.*, *23*, 1185 (1934).

33. ZAUDER, H. L. : *J. Pharmacol. Exptl. Therap.*, ***104***, 11 (1952).
34. FICHTENBERG, D. G. : *Bull. Narcotics*, U.N. Dept. Social Affairs, *3*, No. 4, 28 (1951).
35. FAWAZ, G. : *Proc. Soc. Exptl. Biol. Med.*, *68*, 262 (1948).
36. BERNHEIM, F.; BERNHEIM, M. L. C. : *J. Pharmacol. Exptl. Therap.*, *81*, 374 (1944).
37. BERNHEIM, F.; BERNHEIM, M. L. C. : *ibid.*, *83*, 85 (1945).
38. ADLER, T. K. : *ibid.*, ***106***, 371 (1952).
39. PLOTNIKOFF, N. D.; ELLIOT, H. W.; WAY, E. L.: *ibid.*, ***104***, 377 (1952).
40. YOSIKAWA, N. : *Japan. J. Med. Sci. IV, Pharmacol.*, 12, No. 283; *Proc. Japan. Pharmacol. Soc.*, *13*, 74 (1940).
41. JAGGARD, G. : *Proc. 3rd AORC Meet.*, App. XXIII, page 8 (1949).
42. MORGAN, C. E. : *Proc., 1st AORC Meet.*, 16 (1947).
43. MORGAN, C. E. : *Proc., 5th AORC Meet.*, App. XX, 3 (1951).
44. OESTER, Y. T. : *Proc., 1st AORC Meet.*, 14 (1947).
45. OWENS, F. P. : *Proc., 3rd AORC Meet.*, App. XXVII, Table 2 (1949).
46. OBERST, F. W. : *J. Pharmacol. Exptl. Therap.*, *79*. 266 (1943).
47 WRIGHT, C. I. : *Science*, *92*, 244 (1940).
48. WRIGHT, C. I. : *J. Pharmacol. Exptl. Therap.*, *71*, 164 (1941).
49. WRIGHT, C. I. : *ibid.*, *75*, 328 (1942).
50. ELLIS, S. : *ibid.*, *94*, 130 (1948).
51. MASSART, L.; DUFAIT, R. : *Naturwissenschaften*, *29*, 572 (1941); *Chem. Zentr.*, *1*, 496 (1942).
52. FAILLE, J. : *Recherches chimiques, physiologiques et toxicologiques sur la brucine*, Thesis, National Veterinary School, Alfort; Faculty of Medicine, Paris (1928).
53. ADLER, T. K.; LATHAM, M. E. : *Proc. Soc. Exptl. Biol. Med.*, *73*, 401 (1950).
54. ADLER, T. K.; SHAW, F. H. : *J. Pharmacol. Exptl. Therap.*, ***104***, 1 (1952).
55. MANNERING, G. J.; DIXON, A. C.; BAKER, E. M.; ASSAMI, T. : *ibid.*, *111*, 147 (1954).
56. SANFILIPPO, G. : *Bull. Soc. Ital. Biol. Sper.*, *23*, 1119 (1947).
57. SANFILIPPO, G. : *ibid.*, *24*, 723 (1948).
58. SANFILIPPO, G. : *ibid.*, *29*, 1761 (1953).
59. BRODIE, B. B.; UDENFRIEND, S. : *J. Biol. Chem.*, *158*, 705 (1945).
60. LATHAM, M. E.; ELLIOT, H. W. : *J. Pharmacol. Exptl. Therap.*, *101* 259 (1951).

On the Graphic Formula of Morphine and a Rational Nomenclature of Morphine Derivatives

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It is well known that the constitution of morphine is now fully established after about seventy years of the most skilful chemical investigations crowned by the synthesis of codeine by *Gates et al.* (1).

The usual graphic formula is based upon a phenanthrene skeleton, the middle of which is fused with a piperidine ring. The numbering of the atoms usually follows the classical numbering employed by *Graebe and Liebermann* for the 10 C-atoms in the phenanthrene nucleus (Fig. 1); the remaining four C-atoms are given the numbers 11-14 incl. (*Knorr and Hörlein* (2)). The nitrogen atom generally has no number. This numbering can be found in all the classical papers concerning the structure of morphine and also in the graphic formula proposed by *Cahn and Robinson* (Fig. 8).

Another method of numbering is found in *Patterson and Capell: The Ring Index*, New York 1940, No. 3094, where morphine is considered as being derivative of imino-ethano-phenanthrene-furan (Fig. 2). *Schaumann* (3) has given another graphic formula in which he considered the piperidine nucleus as being the most important analgiphoric group and emphasizes this in the formula (Fig. 3).

The synthesis of morphinan (Figs. 6 and 7) and its derivatives by *Grewe et al.* (4) has given us the nucleus of all compounds in the morphine group; the graphic formula used by these scientists is based upon the old phenanthrene formula for morphine.

Since the middle of the 'thirties it has been the custom (*Wieland and Dane* (5)) to write the phenanthrene nucleus in the steroids (Fig. 4) in a somewhat different manner from the classical formula for phenanthrene used by *Graebe and Liebermann* and also to use another system of numbering. If it is considered necessary to draw the graphic formula for morphine in a new way, it would be natural to base this on the relationship of morphine to the steroids, to accept the numbering used for the steroids, and to take the now fully established stereochemistry of morphine (6) into consideration. We must, however, bear in mind that this involves the drawback that the new numbering does not correspond to the classical numbering used in the numerous papers published over a period of more than sixty years, in which the structure of morphine is developed. The following is an attempt to introduce a new proposal of drawing the morphine formula and to submit a proposal for the nomenclature of compounds in the whole " morphine group ".

The Graphic Formula of Morphine

Morphine is regarded as a phenanthrene derivative and the phenanthrene part of the formula is drawn and numbered in the manner used in steroid chemistry. In order to connote the specific stereochemical configuration, solid lines are used as in steroid chemistry to indicate a position in front of the plane (the paper) and dotted lines to indicate a position behind the plane.

In Fig. 7 these directions are used and it is seen that the morphine molecule contains a morphinan nucleus consisting of the six-membered isocyclic rings A, B and C arranged angularly and a piperidine ring D, having three atoms in ring B. Ring A is a benzene ring; the fully hydrogenated morphinan, where the ring A is a cyclohexane ring is not known at the present time. Due to the benzene ring it would be natural to compare morphinan and morphine with estratrien.

Further, the figure shows that morphine is an epoxy-derivative of morphinan and that the hydroxy group at C_{12} and the oxygen bridge linked to C_{11} are in *cis*-position. The heterocyclic ring D linked to C_9 is in *trans*-position to the two first mentioned groups and must be regarded as a bridge in ring B; the steric configuration for these two rings can be compared with tropane.

By comparison of morphine and estratrien it is seen that in the latter the rings B and C have *trans*-decalin structure while in morphine they have the *cis*-decalin structure.

In the following is given a survey of graphic formulæ for morphinan and morphine with the new (" steroid ") and the classical numbering: Fig. 5: morphinan (" steroid " formula), Fig. 6: morphinan (*Grewe*); Fig. 7: morphine (" steroid " formula) and Fig. 8: morphine (*Cahn-Robinson*). It should be noted that the morphine formula (*Cahn-Robinson*) often is turned through 90° in ring B.

The new " steroid " formula for morphine involves, as mentioned, a numbering which differs from the two old systems used by Cahn-Robinson and by The Ring Index, respectively. The following scheme shows the alterations:

" Steroid formula "	*Cahn-Robinson*	*The Ring Index*
1	4	—
2	3	3
3	2	2
4	1	1
5	11	—
6	10	9
7	9	8
8	14	—
9	13	9c
10	12	—
11	5	4a
12	6	5
13	7	6
14	8	7
15	15	12
16	16	11
(17)	N-(17)	10

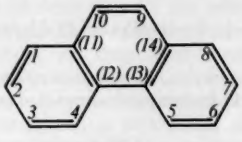

FIGURE 1
Phenanthrene (Graebe and Liebermann)

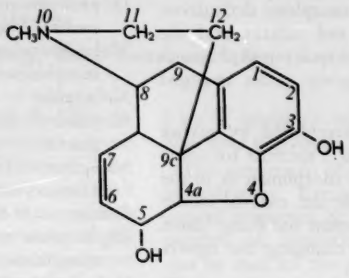

FIGURE 2
Morphine (The Ring Index System)

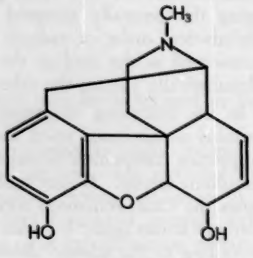

FIGURE 3
Morphine (Schaumann)

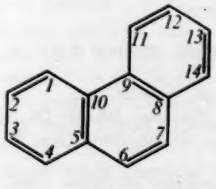

FIGURE 4
Phenanthrene (Wielad and Dane)

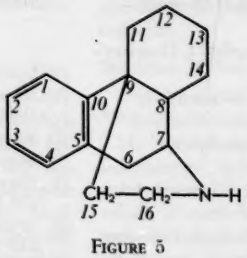

FIGURE 5
Morphinan (" Steroid " formula)

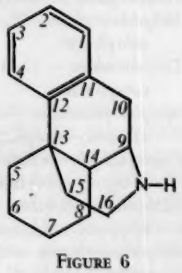

FIGURE 6
Morphinan (Grewe)

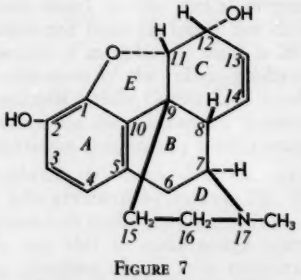

FIGURE 7
Morphine (" Steroid " formula)

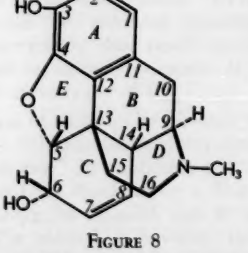

FIGURE 8
Morphine (Cahn and Robinson)

Nomenclature

If we compare the formula of morphine with that of morphinan it is seen that the nucleus in the morphine derivatives is epoxymorphinan, and we are now able to build up a rational nomenclature for the whole group of morphine derivatives, using the generally accepted prefixes and suffixes, and the alphabetical order of radicals (7); since epoxy-morphinan is considered as the nucleus the epoxy group is not arranged alphabetically among the other radicals.

In the following the proposal is exemplified by giving rational names based upon the " steroid " formula for some important compounds belonging to the morphinan or to the morphine group. If one wishes to base the rational names upon the Cahn-Robinson formula or upon the Ring Index formula it can easily be done only by changing the figures according to the scheme above.

Racemorphan = (±)-2-Hydroxy-N-methyl-morphinan.
Levallorphan = N-Allyl-2-hydroxy-morphinan.
Racemethorphan = (±)-2-Methoxy-N-methyl-morphinan.
Tetrahydrodesoxycodeine = 1-Hydroxy-2-methoxy-N-methyl-morphinan.
Desomorphine = 2-Hydroxy-N-methyl-1, 11-epoxy-morphinan.
Dihydromorphine = 2, 12-Dihydroxy-N-methyl-1, 11-epoxy-morphinan.
Dihydrocodeine = 12-Hydroxy-2-methoxy-N-methyl-1, 11-epoxy-morphinan.
Acetyldihydrocodeine = 12-Acetoxy-2-methoxy-N-methyl-1, 11-epoxy-morphinan.
Diacetyldihydromorphine = 2, 12-Diacetoxy-N-methyl-1, 11-epoxy-morphinan.
Methyldihydromorphine = 2, 12-Dihydroxy-12, N-dimethyl-1, 11-epoxy-morphinan.
Dihydromorphinone = 2-Hydroxy-N-methyl-12-oxo-1, 11-epoxy-morphinan.
Dihydrocodeinone = 2-Methoxy-N-methyl-12-oxo-1, 11-epoxy-morphinan.
Metopon = 11, N-Dimethyl-2-hydroxy-12-oxo-1, 11-epoxy-morphinan.
Oxymorphone(Endo) = 2, 8-Dihydroxy-N-methyl-12-oxo-1, 11-epoxy-morphinan.
Dihydrohydroxycodeinone = 8-Hydroxy-2-methoxy-N-methyl-12-oxo-1, 11-epoxy-morphinan.
Methyldesoxymorphine = 12, N-Dimethyl-2-hydroxy-1, 11-epoxy-morphinene-12.
Normorphine = 2, 12-Dihydroxy-1, 11-epoxy-morphinene-13.
Morphine = 2, 12-Dihydroxy-N-methyl-1, 11-epoxy-morphinene-13.
Nalorphine(N-Allylnormorphine) = N-Allyl-2, 12-dihydroxy-1, 11-epoxy-morphinene-13.
Codeine = 12-Hydroxy-N-methyl-1, 11-epoxy-morphinene-13.
Ethylmorphine = 2-Ethoxy-12-hydroxy-N-methyl-1, 11-epoxy-morphinene-13.
Pholcodin (Morpholinyl-ethylmorphine) = 12-Hydroxy-N-methyl-2-(2-morpholinoethoxy)-1, 11-epoxy-morphinene-13.
Dihydrocodeinone enol acetate (Acedicon) = 12-Acetoxy-2-methoxy-N-methyl-1, 11-epoxy-morphinene-12.
Diacetylmorphine = 2, 12-Diacetoxy-N-methyl-1, 11 epoxy-morphinene-13.
Thebaine = 2, 12-Dimethoxy-N-methyl-1, 11-epoxy-morphinadiene-12, 14.

References

(1) Gates, M. *et al.*, *J. Am. Chem. Soc.*, *72*, 228, 4839 (1950); *74*, 1109 (1952).
(2) Knorr, L., and H. Hörlein, *Ber.*, *40*, 3341 (1907).
(3) Schaumann, O., *Arch. exptl. Pathol. Pharmakol.*, *196*, 109, 126 (1940).
(4) Grewe, R. *et al.*, *Naturwissenschaften*, *33*, 333 (1946); *Chem. Ber.*, *81*, 279 (1948).
(5) Wieland, H. and E. Dane, *Hoppe-Seyler's Z. Physiol. Chem.*, *210*, 272 (1932).
(6) Ginsburg, D., *Bull. Narcotics*, U.N. Dep. Social Affairs, 5, No. 4, 32 (1953); J. M. Lindsey and W. H. Barnes, *Acta Cryst. 8*, 227 (1955).
(7) *J. Chem. Soc.*, London, 5699 (1950).

Micro-identification of the Opium Alkaloids

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It is probable that more tests have been described for the opium alkaloids than for any other similar group or organic substances. Their widespread use in medicine, their toxicity, and, above all, their habit-forming properties make their detection in minute quantities a matter of more than academic interest, while the legal significance of the presence of one of these substances makes their absolute identification more important than their exact quantitative estimation. It is the purpose of this paper to review briefly the methods available for the detection of the opium alkaloids when present in microgramme quantities, and to describe the application to these bases of a microtechnique recently elaborated by the authors (Clarke and Williams(1)).

The methods available for the micro-identification of alkaloids may be classified as physical, biological and chemical.

Physical Methods

Physical methods, which have recently been reviewed by Farmilo and Levi (2), although often requiring expensive apparatus, have the distinct advantage that in most cases they do not destroy the material used; this leaves it available for further examination. Consequently, one can employ the entire available sample in a single test, without the subdivision necessary when chemical or biological methods are used. This is not necessarily true, however, for melting-point determination, as some alkaloids are readily decomposed by heat. In any case this method is not really delicate enough for use on the micro-scale, although Fischer and Karawia (3) and Kofler and Muller (4) describe methods using some 50 μg of material.

Numerous methods for the identification and estimation of alkaloids have been based on the optical properties of solutions. Thus, Cahen and Feuer (5) found that they were able to estimate quantities of morphine as small as 20 μg by electrophotometric estimation of the colour produced in a modified Denigès' reaction, while Gettler and Sunshine (6) have described a method for the colorimetric determination of alkaloids in microgramme quantities by methyl orange.

The use of spectrophotometric methods in the ultra-violet region has recently been reviewed by Farmilo (7). There is some difference of opinion as to the sensitivity of the method. Biggs, for example, was able to make rough quantitative estimations of 1 mg quantities of morphine recovered from a Stas-Otto extract, while, replacing the Stas-Otto process by a special extraction technique, Berman and Wright (9) were able determine as little as 1 μg of certain alkaloids. Their method unfortunately fails altogether with some substances, notably morphine and heroin. Identification of alkaloids by means of their infra-red spectra does not appear to have been applied on the microgramme scale (Marion, Ramsay and Jones (10); Pleas, Harley and Wibberley (11).

Little use has been made of fluorescence as a means of identification, although Chase and Pratt (12) have applied it to powdered vegetable drugs, while Hansen (13) states that 1 μg of morphine on filter paper may be recognized by the blue zone it gives in ultra-violet light.

The properties of crystals also provide useful means of identification. Keenan (14), for example, has recorded the optical properties of the crystals of certain derivatives of a number of important alkaloids. Powdered crystals may also be used for the production of X-ray diffraction patterns. This method has high sensitivity; Barnes (15) used 10-μg samples while Gross and Oberst (16) obtained positive results with morphine using less than 1 μg of material.

Paper chromatography affords a further means for the isolation and identification of alkaloids, based on the variation in R_f value. By this method 20 μg or less may be detected (Munier and Macheboeuf (17); Curry and Powell (18)). Borke and Kirch (19) record a similar sensitivity for surface chromatography.

Biological Methods

The biological detection of morphine depends on the " Mauseschwanzphänomen " first recorded by Straub (20). He noticed that mice which had received a subcutaneous injection of morphine exhibited certain definite signs, the most characteristic being the catatonic rigidity of the tail, which is carried in an S-shaped curve. This phenomenon was investigated by Herrmann (21), who showed that the effect was roughly quantitative, the smallest quantity of morphine capable of detection being 5 μg. Other opium alkaloids produced similar effects, although to a widely varying extent.

Maier (22) found that the duration of the " tail reaction " gave an approximate measure of the dose of morphine administered, but that a more accurate estimation could be made by finding the threshold of reaction. By this means, 20 μg of morphine could be estimated quantitatively. Keil and Kluge (23), interpreting their results graphically, found that they were able to estimate quantities of morphine as small as 12 μg with an accuracy of 5%.

The detection of narcotics by bio-assay has been developed by Munch (24, 25), who has used this method for the investigation of " doping " in racehorses. Using a standard technique, he found the threshold for a 20-g. mouse to be 1 μg for heroin, 12 μg for dilaudid, and 60 μg for codeine and morphine. The method is, however, lacking in specificity. Although Munch (24) states that there is a qualitative difference between the effect of morphine and that due to heroin, it is not usually possible to distinguish between closely related substances. The great advantage of the method is the speed with which a result can be obtained. Body fluids such as saliva and urine can be injected directly without the tedious extraction and purification necessary for chemical and physical methods, and even with minimal doses effects become apparent in half an hour.

It is worth noting that Morgan and Gellhorn (26), in a series of experiments designed to compare the sensitivities of biolo-

gical and chemical methods, found that, while the absolute threshold for certain substances (e.g., heroin and dilaudid) is lower for biological methods, in actual application the chemical method was not only more sensitive, but considerably more reliable.

Chemical Methods

The chemical identification of alkaloids may be carried out by means of colour or crystal tests. Both have been in use for over a century; in 1821 Orfila (27) mentioned the shape of morphine crystals, and the red colour produced with nitric acid, while in 1845 Christison (28) gave the ferric chloride and iodic acid tests for morphine, and described the shape of the crystals of the base and of various salts for morphine, codeine and narcotine. Wormley (29) in 1885 gave both colour and crystal tests in some detail. Since then, however, the colour test has become much the more popular. This may be seen by reference to various standard works on toxicology. Autenreith (30), Glaister (31), Kobert (32), Nicholson (33), Sydney Smith and Fiddes (34), Van Oettinger (35), and Witthaus (36) make no mention of crystal tests for the opium alkaloids. Bamford (37), Lucas (38), McNalley (39), Peterson, Haines and Webster (40) and Thienes and Haley (41) give both crystal and colour tests, while the " Methods of Analysis " of the A.O.A.C.* (42) gives crystal tests only.

Both types of test have been described in almost endless variety, Bentley (43) referring to some 50 colour tests for morphine alone, while an even greater number of crystal tests for the various alkaloids of this group have been described by such authors as Vadam (44), Stephenson (45), Fulton (46) and Whitmore and Wood (47). There is little to choose between colour and crystal tests from the point of sensitivity. In the case of the former, with morphine as an example, the limit of the Marquis test is variously put at 1 μg (Hansen (13)), 2 μg (Fulton (48)), or 5 μg (Farmilo, Levi, Oestreicher and Ross (49)). For Froehde's test, Hansen (13) gives 0.1 μg, Wormley (29) 0.6 μg, Farmilo *et al.* (49) 1 μg, and Fulton (50) 0.3 μg, the last-named being for Buckingham's modification of the test. For the crystal test, Fulton (51) puts the limit at 0.1 μg for morphine with iodine reagent M–2, while Lucas (52) gives it as 1 μg or less with Marmé's reagent.

In spite of the popularity of the colour test, and the fact that it is of equal sensitivity, in our opinion the crystal test is by far the more satisfactory. A pure substance, taken in sufficient quantity, may certainly give a series of definite colours with a certain reagent. The same substance, however, when recovered by means of a Stas-Otto extraction, is usually contaminated with material readily charred by sulphuric acid, which masks to a greater or less extent the colours due to the alkaloid. And although purification presents few difficulties when milligrammes are available, on the microgramme scale repeated manipulation tends to reduce the material to vanishing-point. Furthermore, the colour test is subjective, as the transient colour changes may be seen differently by different observers. The crystal test, on the other hand, is objective. The microcrystals are a definite entity and may be photographed for permanent record.

Sensitivities

In comparing the sensitivities of these methods several points must be borne in mind. The usefulness of a test depends not only on its sensitivity, but also on its specificity and its range—i.e., the number of alkaloids for which individual results can be obtained. Some tests are more fully diagnostic than others. Thus, with the physical tests the X-ray diffraction pattern may afford complete identification, whereas the melting-point serves only to confirm a diagnosis already made. Biological tests, as already stated, are almost completely lacking in specificity and the sensitivity claimed for them is apparent rather than real, as no deductions can be drawn from the results of an experiment carried out with a single mouse. In the case of chemical tests the questions of specificity and range depend largely on the choice of reagent which is discussed in detail below.

PRACTICAL PROCEDURE

1. *Crystal Test*

(a) *Reagents*

With crystal tests, identification depends on recognition of the characteristic shape and arrangement of the crystals formed when a suitable reagent is added to a solution of the alkaloid. The success of the test depends to a great extent on the correct choice of reagents. As stated previously, several hundred reagents have been described. In addition to those mentioned by the authors cited above, others are given by Bachmann (53), Denoel and Soulet (54), Duquenois and Faller (55), Fulton and Dalton (56), Janot and Chaigneou (57), Levi and Farmilo (58), Oliverio (59), Putt (60), Rosenthaler (61), Uffelie (62), Wachsmuth (63), Wagenaar (64) and White (65). Use of all these reagents as a general routine is obviously impracticable, as it would entail excessive subdivision of the material available. In selecting the reagents most likely to prove useful, their specificity and range must be considered. Some reagents, such as zinc chloride or sodium nitroprusside, give crystalline derivatives with but few alkaloids. That is to say, their specificity is high but their range limited. Reagents of this type are most useful for confirmatory purposes. Other reagents, such as Reinecke's salt, react with most alkaloids but give crystals so similar in appearance as to be almost useless for purposes of differentiation. Others again, such as platinum chloride and potassium bismuth iodide, react with a reasonable number of alkaloids to give crystals varying so widely in form that they provide a useful basis for identification. This class of reagent is obviously the most useful for routine testing. In practice, we find that the use of some 20 of these reagents is sufficient to identify provisionally all the more common alkaloids. Details of those most useful in the case of the alkaloids of opium are given in Appendix A.

It will be noted that we have abandoned the use of such terms as " Wagner's reagent " and " Marmé's reagent " as, in our opinion, the indiscriminate use of these can lead to considerable confusion.

(b) *Technique*

The micro-technique recently introduced by the authors (1) is carried out as follows:* The test material is dissolved in 1% acetic acid or hydrochloric acid. A microdrop (volume approximately 0.1 cu. mm.) of this solution is transferred to a cover slip by means of a glass rod 1 mm. in diameter. A similar drop of reagent is added and the two mixed. The cover slip is inverted and placed on a cavity slide where it rests on thin glass distance pieces cemented on either side of

* Association of Official Agricultural Chemists (Ed. note).

* See Fig. 1.

Table 1

Alkaloid	Gold bromide	Lead iodide	Mercuric chloride	Platinum chloride	Platinum iodide	Pot. bismuth iodide	Pot. cadmium iodide	Potassium chromate	Potassium iodide	Pot. mercury iodide	Pot. tri-iodide (1)	Pot. tri-iodide (2)	Pot. tri-iodide (3)	Sodium carbonate	Sodium nitroprusside
Apomorphine	X	a	a	a	a	X	a	a	a	X	o	a	o	a	a
Benzylmorphine	a	X	a	a	a	a	a	a	X	a	a	X	a	X	a
Codeine	a	X	X	a	a	a	X	—	X	X	X	—	X	—	o
Cotarnine	X	X	X	X	o	a	a	—	—	X	X	o	X	—	—
Dihydrocodeine	—	—	o	—	a	X	o/a	—	—	a	o	—	o	—	—
Dihydrocodeinone	a	X	X	a	a	X	a	—	—	a	a	X	o/a	—	o
Dihydrohydroxycodeinone	a	—	o	X	—	a	a	—	—	a	X	—	o/a	X	—
Dihydromorphine	a	—	o	a	X	a	o	—	—	X	o	—	o	—	—
Dihydromorphinone	a	—	o	a	a	a(X)	a	—	—	a	o	—	o	—	X
Ethylmorphine	a	—	X	a	a	a	X	—	—	X	—	—	X	—	—
Ethylnarceine	a	a	o	a	o	a	o/a	X	X	a	o	X	o	o	o
Heroin	a	a	X	X	a	X	a	X	—	a	o/a	—	o/a	X	o
Morphine	a	—	X	o	a	X	X	X	—	a(X)	X	—	o	—	—
Narceine	a	X	X	X	o	a	o	X	X	o/a	o	X	o	—	—
Narcotine	a	X	o/a	a	a	a	a	X	o	a	o/a	a	o/a	X	o
Néopine	a	—	X	—	a	a	X	—	—	X	X	—	X	—	—
Papaverine	a	o/a	X	X	a	a	X	o	X	X	a	X	a	o	o
Pseudomorphine	a	X	X	X	X	X	a	o/a	X	a	a	X	a	—	X
Thebaine	a	o/a	o/a	X	o/a	a	a	a	o	a	a	—	a	X	o/a

X = Crystals; a = Amorphous; o = Oil droplets; o/a = Oily amorphous; a(X) = Crystals form from more dilute solutions; — = No precipitate.

the depression as shown in the diagram. The hanging drop is now examined under the microscope. As soon as a precipitate can be seen, the cover slip is ringed with 25% gum-arabic solution to prevent further evaporation. The drop is then examined every few hours and its appearance noted when crystallization is complete. This may take 24 hours or more. Once tentative identification has been made, similar crystals should be prepared from a known sample of the alkaloid and compared with those from the test solution. It is essential that all glassware should be well cleaned and thoroughly rinsed, as traces of synthetic detergents may interfere with precipitation (Casidio and Gallo (66), Janot, Goutarel and Decay (67)).

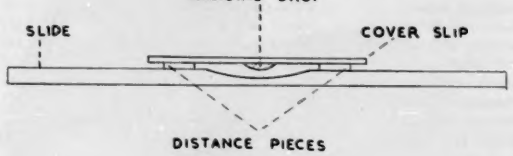


FIGURE 1

(c) *Results*

Table 1 shows the results obtained by treating some of the more important opium alkaloids with fifteen different reagents, under comparable conditions. In each case a microdrop of a 1% solution of the alkaloid (containing 1 µg) was mixed with a similar drop of reagent. The slide was sealed immediately to prevent evaporation and the appearance recorded after twenty-four hours.

Table 2 gives the appearance of the crystals and the sensitivity of the test, the latter quantity being the minimum amount of alkaloid required to give recognizable crystals. In order to obtain these figures serial dilutions of the alkaloid were employed, sealing of the slide being deferred until the drop had been concentrated by evaporation.

Some of the crystals obtained are shown in Plates 1-12, the weight of material used in the test being indicated.

2. *Colour Tests*

As already stated, in our opinion colour tests are less reliable than crystal tests, although they have considerable value for confirmatory purposes. Details of these tests are given by such authors as Bamford (38), Fulton (50), Jackson (68), Pesez (69) and Taylor (70).

The most widely used colour reactions are those in which a solution of some substance in concentrated sulphuric acid is added to a minute portion of the solid alkaloid and the resulting colour changes noted. Many substances have been suggested for this purpose, the more important including formaldehyde (Marquis (71)), ammonium molybdate (Froehde (72)), selenious acid (Mecke (73), Lafon (74)), p-dimethylaminobenzaldehyde (Wasicky (75)), sodium tungstate (Reichard (76)), titanium dioxide (Flueckiger (77)), and sucrose (Schneider (78), Weppen (79)).

As we have reported previously (1), we find that the sensitivity of most of these tests can be increased if the following procedure be adopted, Froehde's test being taken as an example. A microdrop of the test solution is placed on an opal-glass plate and a similar drop of a 0.5% aqueous solution of ammonium molybdate added. After evaporation, a microdrop of concentrated sulphuric acid is applied to the residue, and the colour changes noted. In the same way the tests ascribed to Mecke, Reichard and Schneider-Weppen may be carried out with aqueous solutions containing 0.5% of selenious acid, 1% sodium tungstate and 10% of sucrose respectively. For Wasicky's test a 10% solution of p-dimethylaminobenzaldehyde in glacial acetic acid is used.

Table 2

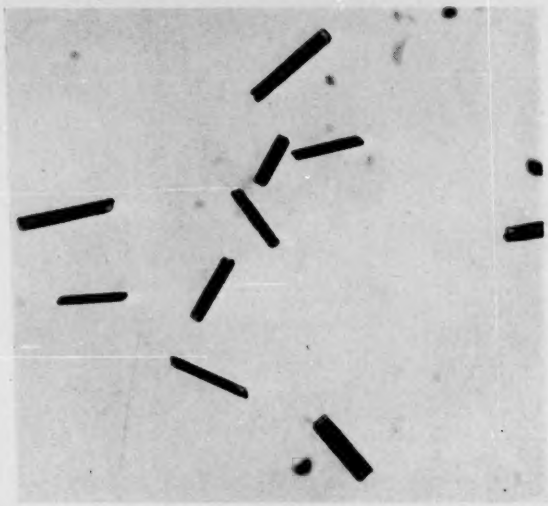
Reagent	Appearance of crystals	Sensitivity (µg)
Apomorphine		
Gold bromide	Serrated crosses	0.0005
Potassium bismuth iodide	Rosettes of dark needles	0.005
Potassium mercury iodide	Bunches of needles	0.05
Benzylmorphine		
Lead iodide	Hedgehogs (2 days)	0.25
Sodium carbonate	Rosettes of rods	0.05
Potassium tri-iodide (2)	Rosettes of plates (2 days)	0.25
Potassium iodide	Rosettes of needles or plates	0.025
Codeine		
Potassium tri-iodide (1)	Feathery rosettes	0.05
Potassium cadmium iodide	Small rosettes—small plates	0.01
Potassium mercury iodide	Irregular plates	0.025
Lead iodide	Rosettes of rods (2 days)	0.5
Mercuric chloride	Irregular needles in bunches	0.25
Potassium iodide	Rosettes of needles	1.0
Potassium tri-iodide (3)	Dense rosettes	0.25
Cotarnine		
Platinum chloride	Rods	0.025
Mercuric chloride	Bunches of needles	0.05
Gold bromide	Yellow rods	0.1
Potassium tri-iodide (1)	Very small plates	1.0
Potassium tri-iodide (3)	Small rods	0.005
Potassium mercury iodide	Irregular plates	0.05
Lead iodide	Needles or dendrites	0.25
Dihydrocodeine		
Potassium bismuth iodide	Bunches of hexagonal plates	0.005
Dihydrocodeinone		
Mercuric chloride	Dense rosettes	0.05
Potassium tri-iodide (2)	Very long rods (2 days)	0.25
Lead iodide	Dense rosettes (2 days)	0.1
Potassium bismuth iodide	Rhomboidal plates	0.01
Dihydrohydroxycodeinone		
Potassium tri-iodide (1)	Small dark plates	0.0025
Sodium carbonate	Long thin needles	0.025
Platinum chloride	Rosettes of rods	0.25
Dihydromorphine		
Platinum iodide	Smudge rosettes	0.025
Potassium mercury iodide	Sheaves of fine needles	0.1
Dihydromorphinone		
Sodium nitroprusside	Rods	0.5
Potassium bismuth iodide	Grain-like crystals (2 days)	0.05
Ethyl morphine		
Mercuric chloride	Long blades	1.0
Potassium mercury iodide	Smudge rosettes	0.05
Potassium cadmium iodide	Smudge rosettes (2 days)	0.1
Potassium tri-iodide (3)	Bunches of feathery needles	0.05
Ethyl narceine		
Potassium iodide	Rosettes of rods	0.025
Potassium chromate	Bunches of rods	0.1
Potassium tri-iodide (2)	Rosettes of rods	0.05
Heroin		
Platinum chloride	Rosettes	0.25
Potassium bismuth iodide	Small dense rosettes (2 days)	0.005
Mercuric chloride	Fine dendrites	0.1
Potassium chromate	Smudge rosettes (hedgehogs)	0.1
Sodium carbonate	Rosettes of plates	1.0
Morphine		
Potassium cadmium iodide	Sheaves of fine needles	0.01
Potassium tri-iodide (1)	Plates	0.1
Mercuric chloride	Bunches of needles	0.1
Potassium bismuth iodide	Small rods and plates	0.01
Potassium mercury iodide	Tufts of thread-like crystals	0.05
Potassium chromate	Small plates	0.5
Narceine		
Platinum chloride	Rosettes of blades	0.25
Mercuric chloride	Small rosettes	0.25
Lead iodide	Thread-like crystals	0.1
Potassium chromate	Tufts of needles	0.1
Potassium tri-iodide (2)	Rosettes of needles	0.025
Potassium iodide	Fine needles	0.025
Narcotine		
Sodium carbonate	Rosettes and bunches of needles	0.025
Potassium chromate	Rosettes	0.1
Lead iodide	Rosettes of fine branching needles	0.25
Neopine		
Potassium cadmium iodide	Silvery rosettes—plates	0.025
Potassium mercury iodide	Oily rosettes	0.025
Potassium tri-iodide (3)	Small plates or rosettes	0.1
Potassium tri-iodide (1)	Rosettes of feathery needles	0.05
Mercuric chloride	Bunches of plates, rods and needles	0.25
Papaverine		
Platinum chloride	Yellow plates (2 days)	0.05
Potassium iodide	Irregular plates	0.025
Potassium mercury iodide	Plates and squares	0.05
Potassium tri-iodide (2)	Small rosettes	0.1
Potassium cadmium iodide	Rosettes of blades	0.025
Mercuric chloride	Very small needles	0.25
Pseudomorphine		
Potassium iodide	Petal-shaped crystals	0.01
Platinum iodide	Small dark rosettes (2 days)	0.25
Platinum chloride	Small rods	0.025
Lead iodide	Squares	0.025
Potassium bismuth iodide	Rhomboids and rods (2 days)	0.05
Potassium tri-iodide (2)	Plates	0.05
Mercuric chloride	Smudge rosettes—rods and plates	0.1
Sodium nitroprusside	Plates	0.1
Thebaine		
Sodium carbonate	Rosettes of small plates	0.025
Platinum chloride	Dense rosettes	0.05

This modification is not practicable for Marquis' test or Flueckiger's test, which are carried out by treating the residue left by evaporating a microdrop of the test solution with a trace of the original reagent—namely, a mixture of one part of 40% formaldehyde solution with twenty parts of concentrated sulphuric acid for the former and a 0.5% solution of titanium dioxide in concentrated sulphuric acid for the latter.

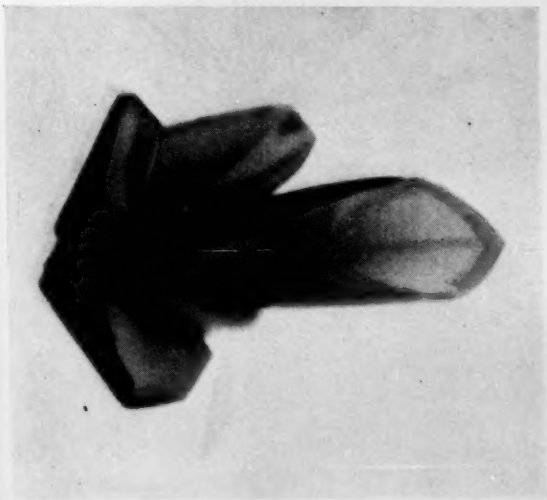
Carried out in the above manner, these tests have sensitivities ranging from 1 µg to 0.025 µg, although the colour changes observed are not always the same as when larger quantities are employed. The colours obtained for 1 µg quantities of a number of alkaloids together with the absolute sensitivities are given in Table 3. It should be noted that with minimal quantities it is seldom that the whole range of colours is observed.

Examples of the crystals obtained with various reagents

1. *Apomorphine* (0.001 µg) *with gold bromide* — × 600.

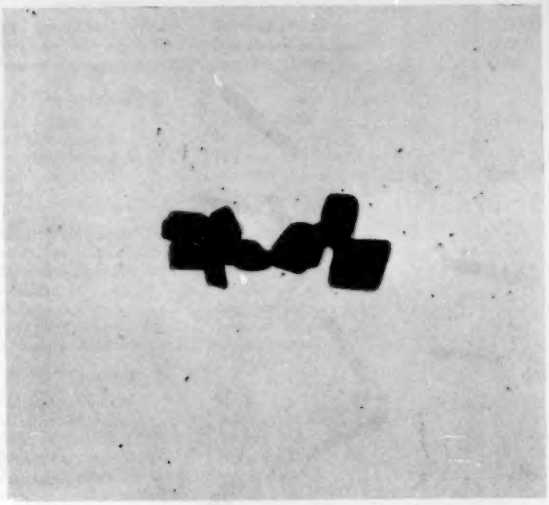


2. *Cotarnine* (0.025 µg) *with gold bromide* — × 300.



3. *Dihydrocodeine* (0.025 µg) *with potassium bismuth iodide* — × 400.

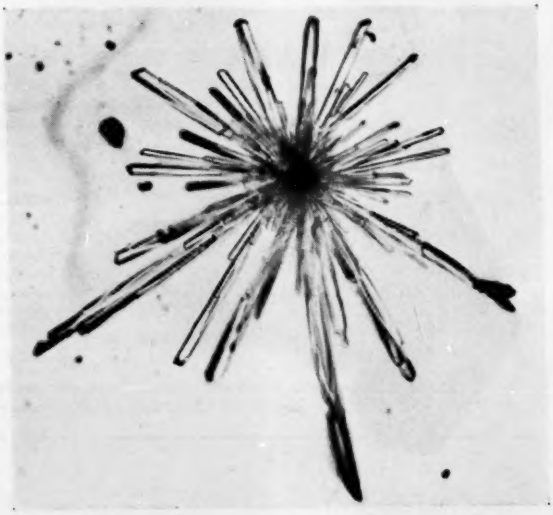
4. *Dihydrocodeinone* (0.025 µg) *with potassium bismuth iodide* — × 100.



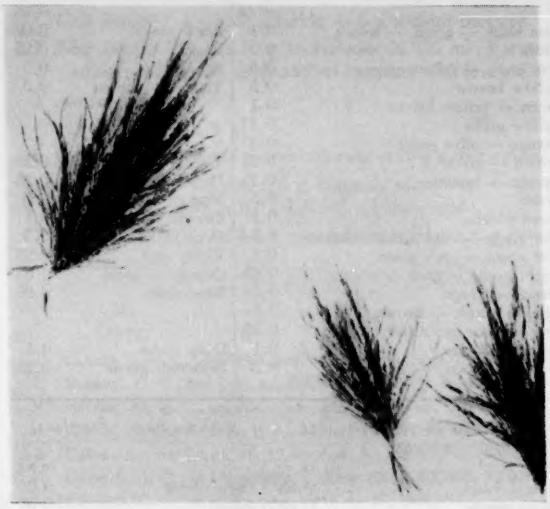
5. *Dihydrohydroxycodeinone* (0.01 µg) *with potassium tri-iodide* (1) — × 300.

6. *Dihydromorphinone* (0.1 µg) *with potassium bismuth iodide* — × 300.

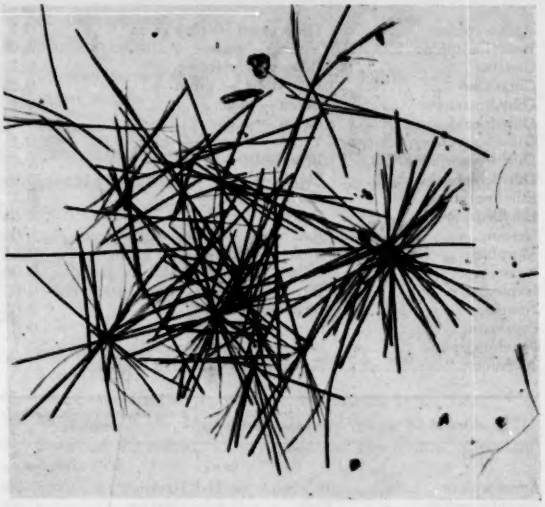
7. *Ethyl morphine* (0.1 µg) *with potassium tri-iodide* (3) — × 100.



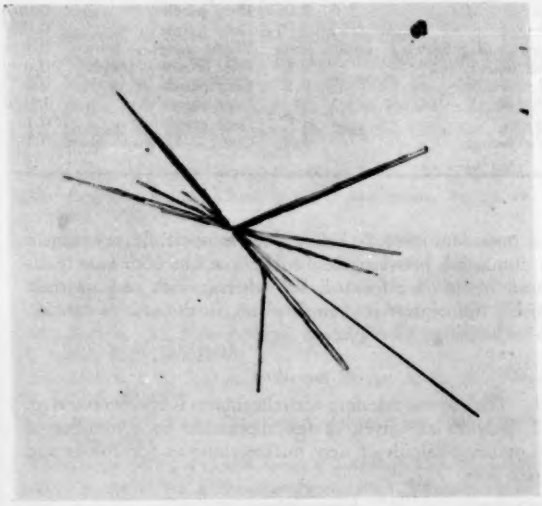
8. *Ethyl narceine* (0.1 µg) *with potassium iodide* — × 300.



9. *Morphine* (0.025 µg) *with potassium cadmium iodide* — × 100.



10. *Narceine* (0.05 µg) *with potassium tri-iodide* (2) — × 75.



11. *Narcotine* (0.1 µg) *with sodium carbonate* — × 100.

12. *Pseudomorphine* (0.05 µg) *with potassium iodide* — × 300.

Table 3

Alkaloid	*Ammonium molybdate (Froehde)*		*Selenious acid (Mecke)*		*Sodium tungstate (Reichard)*	
		in μg		*in μg*		*in μg*
Apomorphine	Deep green — blue green	0.1	Blue black — green — brown	0.1	Black violet	0.025
Benzylmorphine	Violet — green	0.05	Green	0.1	Violet	0.25
Codeine	Blue, slowly fading	0.1	Blue green — yellow green — brown	0.5	Pale violet	0.5
Cotarnine	Pale violet — green	0.25	Yellow brown	0.5	Yellow — brown	0.5
Dihydrocodeine	Green — blue	0.1	Green — yellow brown	0.1	———	
Dihydrocodeinone	Green — blue	0.1	Yellow green	0.25	———	
Dihydrohydroxycodeinone	Yellow — green — blue	0.1	Orange — olive green	0.25	———	
Dihydromorphine	Blue violet	0.025	Brown — green	0.25	Violet	0.25
Dihydromorphinone	Purple — blue — green	0.05	Orange — brown	0.25	Dark brown	0.25
Ethylmorphine	Green — blue	0.1	Green	0.5	Blue violet	0.5
Ethylnarceine	Green — blue	0.05	Green — blue	0.1	Orange — green	0.1
Heroin	Red violet — blue — light green	0.05	Blue green — olive green — brown	0.5	Deep violet	0.5
Morphine	Violet — blue — light green	0.05	Blue green — grey green	0.1	Violet	0.25
Narceine	Brown — grey — blue — green	0.05	Bright green — grey — orange	0.25	Orange — green	0.05
Narcotine	Brown — green — blue — pale green	0.05	Green — orange	0.25	Blue violet	0.25
Neopine	Blue — green	0.05	Reddish purple — brown	0.1	———	
Papaverine	Faint green — blue	0.5	Grey — grey green fading	0.25	———	
Pseudomorphine	Blue — violet — green	0.1	Purple — brown	0.1	Deep violet	0.1
Thebaine	Greenish brown — red brown	0.1	Green — brown — orange	0.25	Brownish green	0.25

Alkaloid	*Sucrose (Schneider-Weppen)*		*p-dimethylamino benzaldehyde (Wasicky)*		*Formaldehyde (Marquis)*		*Titanium dioxide (Flueckiger)*	
		in μg		*in μg*		*in μg*		*in μg*
Apomorphine	Brown	0.25	Red	0.25	Purple — black	0.05	Deep purple	0.05
Benzylmorphine	Pink	0.5	Orange	0.25	Red — purple	0.025	Purple	0.05
Codeine	Pink	0.5	Orange	0.25	Violet	0.05	———	
Cotarnine	Orange	0.5	———		———		Yellow — brown	0.5
Dihydrocodeine	Pink	0.5	Orange	0.25	Purple	0.1	———	
Dihydrocodeinone	Pink	1.0	Orange	0.5	Yellow — brown — purple	0.25	———	
Dihydrohydroxycodeinone	Pink	1.0	Faint orange	0.1	Yellow — brown — purple	0.5	———	
Dihydromorphine	Pink	0.25	Bright orange	0.25	Red purple	0.025	Deep purple	0.025
Dihydromorphinone	Pink	1.0	Orange	0.25	Yellow — red — purple	0.25	Deep purple	0.025
Ethylmorphine	Pink	1.0	Bright orange	0.1	Yellow — purple — black	0.1	———	
Ethylnarceine	Yellow	0.5	Yellow	0.5	Brown — green — blue	0.1	Orange — brown	0.1
Heroin	Pink	0.5	Orange	0.1	Violet	0.05	Deep purple	0.025
Morphine	Pink	0.25	Orange	0.1	Violet	0.05	Deep purple	0.025
Narceine	Yellow	0.25	Yellow	0.25	Brown — deep brown — green	0.05	Bright orange — brown	0.1
Narcotine	Brown	0.1	Yellow	0.25	Bluish violet fading	0.1	Faint brown — purple	0.5
Neopine	Pink	0.25	Orange	0.1	Blue violet	0.1	Faint purple	0.5
Papaverine	Brown	0.1	———		———		Faint purple	1.0
Pseudomorphine	Green	1.0	———		Rose red	0.1	Deep purple	0.1
Thebaine	Brown	0.025	Brown	0.25	Red — orange	0.05	Green — brown — black	0.1

Discussion

The "smallest detectable quantity" of any substance depends on a number of factors including the efficiency of the extraction process employed, the number of different tests that must be carried out and the sensitivities of these tests. Leaving the first of these factors out of consideration and assuming the second to have been reduced to a minimum by correct choice of reagents, it is obvious that any technique that increases the sensitivity of the test causes a corresponding decrease in the amount that can be identified. As the results tabled above show at least one crystal test with a sensitivity of 0.05 μg for each alkaloid mentioned, it follows that, under favourable circumstances, one should be able to identify quantities of the order of a microgramme of any of these substances, provided that they are in a reasonable state of purity.

Although most of these alkaloids may be identified without difficulty, it is not easy to differentiate between codeine and neopine. This might be expected from their structures, which differ only in the position of a double bond. We find that potassium mercury iodide is the most satisfactory reagent to distinguish between these substances. In both cases gelatinous rosettes are formed, but whereas with codeine these quickly disintegrate into small plates, in the case of neopine no such change takes place.

Summary

1. The literature dealing with the subject is briefly reviewed.
2. Results are given of the application to a number of the opium alkaloids of new microtechniques for colour and crystal tests.

Acknowledgements

We wish to express our thanks to Professor E. C. Amoroso for his help and encouragement and to Mr. R. F. S. Creed and Mr. H. Burgess for taking the photographs. We acknowledge gratefully gifts of alkaloids from Messrs. T. and H. Smith Ltd., and Messrs. J. F. MacFarlan and Co. Ltd. We are also much indebted to Miss Ann Stanley for technical assistance.

APPENDIX A

Reagents for microcrystalline tests

(Unless otherwise indicated, the quantities shown are dissolved in 100 ml of water)

1. *Gold bromide :* 5 g gold chloride + 5 g sodium bromide.
2. *Lead iodide :* Dissolve 30 g lead acetate in 100 ml of water, adjust to pH 6 with acetic acid, and saturate with lead iodide.
3. *Mercuric chloride :* 5 g.
4. *Platinum chloride :* 5 g.
5. *Platinum iodide :* 5 g platinum chloride + 25 g sodium iodide.
6. *Potassium bismuth iodide :* 5 g bismuth subnitrate + 25 g potassium iodide in 100 ml of 2% sulphuric acid.
7. *Potassium cadmium iodide :* 1 g cadmium iodide + 2 g potassium iodide.
8. *Potassium chromate :* 5 g.
9. *Potassium iodide :* 5 g.
10. *Potassium mercury iodide :* 1.5 g mercuric iodide + 5 g potassium iodide.
11. *Potassium tri-iodide* (1) *:* 2 g iodide + 4 g potassium iodide.
12. *Potassium tri-iodide* (2) *:* 0.1 g iodine + 0.2 g potassium iodide.
13. *Potassium tri-iodide* (3) *:* 1 g iodine + 50 g potassium iodide.
14. *Sodium carbonate :* 5 g.
15. *Sodium nitroprusside :* 1 g.

REFERENCES

1. CLARKE, E. G. C., and WILLIAMS, M., *J. Pharm. Lond. VII*, 255, 1955.
2. FARMILO, C. G., and LEVI, L., *Bull. Narcotics V* (4), 20, 1953.
3. FISCHER, R., and KARAWIA, M. S., *Mikrochem. Acta*, 366, 1953.
4. KOFLER, L., and MÜLLER, F. A., *Mikrochemie, 22*, 43, 1937.
5. CAHEN, R., and FEUER, H., *C. R. Acad. Sci., 208*, 1907, 1939.
6. GETTLER, A. O., and SUNSHINE, I., *Anal. Chem., 23*, 779, 1951.
7. FARMILO, C. G., *Bull. Narcotics, VI* (3–4), 18, 1954.
8. BIGGS, A. I., *J. Pharm. Lond. IV*, 547, 1952.
9. BERMAN, E., and WRIGHT, H. N., *A. M. A. Arch. industr. Hyg., 8*, 518, 1953.
10. MARION, L., RAMSAY, D. A., and JONES, R. N., *J. Amer. Chem. Soc., 73*, 305, 1951.
11. PLEAT, G. B., HARLEY, J. H., and WIBBERLY, S. E., *J. Amer. pharm. Ass. Sci. Ed., 40*, 107, 1951.
12. CHASE, C. R., and PRATT, R., *J. Amer. pharm. Ass. Sci. Ed., 38*, 324 1949.
13. HANSON, A., *Svensk. kem. Tidskr., 58*, 10, 1946.
14. KEENAN, G. L., *Chem. Anal., 39*, 33, 52, 79, 1950; *ibid., 40*, 4, 28, 1951.
15. BARNES, W. H., *Bull. Narcotics, VI* (1), 20 (2), 27, 1954.
16. GROSS, S. T., and OBERST, F. W., *J. Lab. clin. Med., 32*, 94, 1947.
17. MUNIER, R., and MACHEBŒUF, M., *Bull. Soc. Chim. biol., 31*, 1144, 1949.
18. CURRY, A. S., and POWELL, H., *Nature*, Lond., *173*, 1143, 1954.
19. BORKE, M. L., and KIRCH, E. R., *J. Amer. pharm. Ass. Sci. Ed. 42*, 627, 1953.
20. STRAUB, W., *Dtsch. med. Wschr., 37*, 1462, 1911.
21. HERMAN, O., *Biochem. Z., 39*, 216, 1912.
22. MAIER, L., *Arch. exp. Path. Pharmak., 161*, 163, 1931.
23. KEIL, W., and KLUGE, A., *Arch. exp. Path. Pharmak., 174*, 493, 1934.
24. MUNCH, J. C., *J. Amer. pharm. Ass. Sci. Ed. XXIII*, 766, 1185, 1934; *ibid., XXIV*, 557, 1935.
25. MUNCH, J. C., SLOANE, A. B., and LATVEN, A. R., *Bull. Narcotics, IV* (3), 23, 1952.
26. MORGAN, C. E., and GELLHORN, A., *Industr. Engng. Chem.* (*Anal.*), *19*, 806, 1947.
27. ORFILA, M. P., *A General System of Toxicology*, Cox, Lond., 1821.
28. CHRISTISON, R., *A Treatise on Poisons*, Black, Edinburgh, 1845.
29. WORMLEY, T. G., *Microchemistry of Poisons*, Lippincott, Philadelphia, 1885.
30. AUTENREITH, W., *Detection of Poisons*, Churchill, Lond., 1928.
31. GLAISTER, J., *Medical Jurisprudence and Toxicology*, Livingstone, Edinburgh, 1950.
32. KOBERT, R., *Lehrbuch der Intoxikation*, Ferdinand Enke, Stuttgart, 1902.
33. NICHOLSON, J. A., *Lander's Veterinary Toxicology*, Ballière, Tindall & Cox, Lond., 1945.
34. SYDNEY SMITH, and FIDDES, F. S., *Forensic Medicine*, Churchill, Lond., 1949.
35. VON OETTINGEN, W. F., *Poisoning*, Heinemann, Lond., 1952.
36. WITTHAUS, R. A., *Manual of Toxicology*, Wood, New York, 1911.
37. BAMFORD, F., *Poisons, Their Isolation and Identification*. Churchill, Lond., 1951.
38. LUCAS, A., *Forensic Chemistry*, Arnold, Lond., 1945.
39. MCNALLY, W. D., *Medical Jurisprudence and Toxicology*, Saunders, Lond., 1939.
40. PETERSON, F., HAINES, W. S., and WEBSTER, R. W., *Legal Medicine and Toxicology*, Vol. II, Saunders, Lond., 1923.
41. THIENES, C. H., and HALEY, T. J., *Clinical Toxicology*, Kimpton, Lond., 1948.
42. *Official Methods of Analysis*, Ass. Off. Agric. Chem. Wash. Washington, D. C., 1950.
43. BENTLEY, K. W., *The Chemistry of the Morphine Alkaloids*, Clarendon, Oxford, 1954.
44. VADAM, M., *J. Pharm. Chim., 4*, 485, 1896; *ibid., 5*, 100, 1897.
45. STEPHENSON, C. H., *Some Micro-chemical Tests for Alkaloids*, Griffin, Lond., 1921.
46. FULTON, C. C., *Amer. J. Pharm., 104*, 244, 1932; *ibid., 112*, 51, 134, 1940.
47. WHITMORE, W. F., and WOOD, C. A., *Mikrochemie, 27*, 249, 1939.
48. FULTON, C. C., *Amer. J. Pharm., 109*, 219, 1937.
49. FARMILO, C. G., LEVI, L., OESTREICHER, P. M. L., and ROSS, R. J. *Bull. Narcotics IV* (4), 16, 1952.
50. FULTON, C. C., *J. Lab. clin. Med., 23*, 625, 1938.
51. FULTON, C. C., *J. Lab. clin. Med., 23*, 622, 1938.
52. LUCAS, G. K. W., *Canad. J. Res., 28*, B, 37, 1950.
53. BACHMANN, G., *Pharm. Ztg., 84*, 305, 1948.
54. DENOEL, A., and SOULET, U., *J. Pharm. Belg., 1*, 34, 50, 66, 1942.
55. DUQUENOIS, P., and FALLER, Mlle, *Bull. Soc. chim. Fr., 6*, 998, 1939.
56. FULTON, C. C., and DALTON, J. B., *J. of Crim. Law and Criminology, 32*, 358, 1941.
57. JANOT, M., and CHAIGNEOU, M., *C. R. Acad. Sci., 229*, 69, 1949.
58. LEVI, L., and FARMILO, C. G., *Canadian J. of Chem., 30*, 783, 1952.
59. OLIVERIO, A., *Ann., Chim., appl., 28*, 353, 1938.
60. PUTT, E. B., *J. industr. Engng. Chem., 4*, 508, 1912.
61. ROSENTHALER, L., *Arch. Pharm. CCLXV*, 319, 1927.
62. UFFELIE, O. F., *Chem. Weekbl., 41*, 101, 1945.
63. WACHSMUTH, H., *J Pharm. Belg., 8*, 283, 1953.
64. WAGENAAR, G. H., *Pharm. Weekbl., 76*, 276, 1939.
65. WHITE, E. P., *Industr. Engng. Chem.* (*Anal.*), *13*, 509, 1941.
66. CASADIO, S., and GALLO, U., *Boll. chim.-farm., 91*, 177, 1952.
67. JANOT, M. M., GOUTAREL, R., and DECAY, A., *Ann. pharm. franç., 5*, 267, 1947.

68. JACKSON, K. E., *Industr. Engng. Chem. (Anal.), 10,* 380, 1938.
69. PESEZ, M., *Ann. Chim. anal., 24,* 153, 1942.
70. TAYLOR, F. O., *Allen's Commercial Organic Analysis, VII, 665,* Churchill, Lond., 1929.
71. MARQUIS, *Z. anal. Chem., 38,* 467, 1899.
72. FROEHDE, A., *Arch. Pharm., 176,* 54, 1866.
73. MECKE, *Z. Off. Chem., 5,* 351, 1899, cited in *Merck's Index.* Merck & Co., Inc., Rahway, N.J., 5th Ed., 1940. Original reference not available.
74. LAFON, *C. R. Acad. Sci. C.,* 1543, 1886.
75. WASICKY, *Z. anal. Chem., 54,* 394, 1915.
76. REICHARD, *Z. anal. Chem., 42,* 95, 1903.
77. FLUECKIGER, F. A., Feb. 1880, cited in the *Dispensatory of the U.S.A.,* edited by Remington *et al.,* Lippincott, Philadelphia, 20th Ed., 1918.
78. SCHNEIDER, R., *J. prakt. Chem.* (2) 6, 455, 1873.
79. WEPPEN, *Arch. Pharm., 205,* 112, 1874.

The Reaction of 3-Hydroxy-N-Methylmorphinan (Dromoran®) with Chloroplatinic Acid

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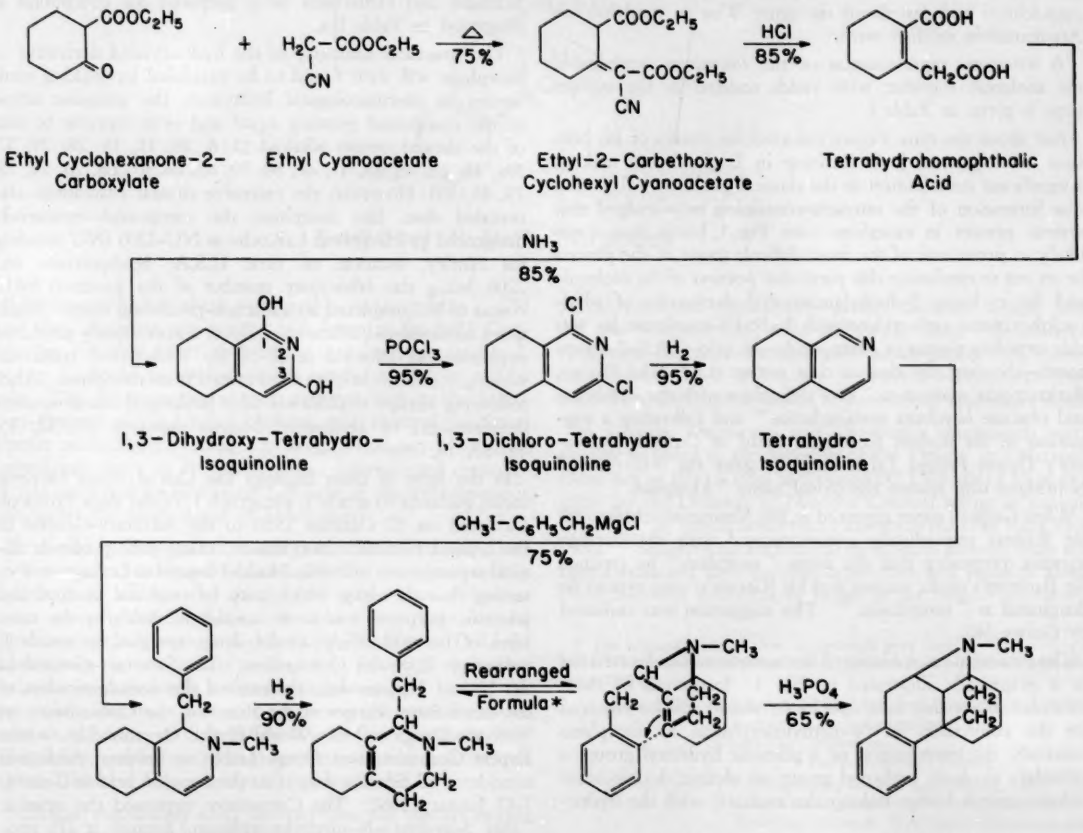
ABSTRACT

When 3-hydroxy-N-methylmorphinan interacts with chloroplatinic acid in aqueous ethanol a complex having the composition $[C_{17}H_{23}NO.H]_2.[PtCl_6]$ precipitates on standing. Product yields are dependent upon the pH of the medium and availability of the alkaloidal cation is most likely the rate-controlling step in the metathetical process of complex formation. The reaction is highly sensitive and under suitable conditions as little as 1γ of the amine can still be readily detected. It fails with opium alkaloids of closely related structures which emphasizes its value as a specific microchemical method for identifying the synthetic narcotic. The X-ray diffraction pattern, ultraviolet and infrared absorption spectra, the dissociation constant and solubility beha-

TABLE I

Synthesis of N-Methylmorphinan according to Grewe



* Heavy lines indicate heterocyclic unit of the molecule and arrow shows mode of ring closure involving the benzene nucleus and the unsaturated fused ring system to form an angular phenyl group. As far as the author is aware, no analogy can be found in the literature for this interesting reaction, which comes close to Robinson's theoretical concepts regarding the synthesis of morphine by the opium poppy (41a).

viour of the complex are reported and these data utilized to interpret characteristic structural features of the alkaloid and its derivative. The constants thus derived are also of value for the determination of minute amounts of the narcotic drug.

Historical Review

On 21 October 1946, an important paper was presented by R. Grewe to a group of distinguished chemists assembled in the city of Göttingen. After seven years of strenuous research on the synthesis of morphine (39, 40) the famous scientist had succeeded in preparing a compound whose structure came closer to the model than any other synthetic known at that time. The compound was " 2-methyl-5,9-tetramethylene-6,7-benzo-2-aza-bicyclo-(3,3,1)-nonene-6 ". Grewe called it briefly " Morphan ", so as to express more strikingly its fundamental resemblance to morphine, and regarding the importance of the chemical process itself he made the following prediction : " Man darf vermuten, dass die neue synthetische Methode die Darstellung zahlreicher Substanzen vom Morphin-Typ erlauben wird, die sich durch eine besondere pharmakologische Wirkung auszeichnen und dass damit ein neuer Weg zu synthetischen Arzneimitteln eröffnet wird."

A schematic representation of the ingenious synthesis of the molecule together with yields realized in the various steps is given in Table I.

Just about the time Grewe reported the results of his brilliant investigations, J. A. Barltrop in England was making a significant contribution to the classical problem. Believing that formation of the nitrogen-containing *meta*-bridged ring system present in morphine—see Fig. 1, heavy lines—was likely to prove one of the most difficult stages of the process he set out to synthesize this particular portion of the molecule and by cyclizing β-diethylaminoethyl derivatives of ethyl-cyclohexanone carboxylate with 1-alkyl-β-tetralones he was able to isolate a series of compounds—bicyclo-(3,3,1)-2-azanonanes—showing the desired ring system (1).* Like Grewe, Barltrop was anxious to " save difficulties with the cumbrous and obscure *bicyclo*aza nomenclature " and following a suggestion of Sir Robert Robinson, Head of Oxford University's Dyson Perrins Laboratory, he gave the 9-membered N-bridged ring system the trivial name " Morphan ".

When Grewe's paper appeared in *Die Naturwissenschaften* (38) Sir Robert immediately communicated with the German scientist, proposing that the name " morphan " be retained for Barltrop's cyclic amines and his (Grewe's) ring system be designated as " morphinan ". This suggestion was endorsed by Grewe (40).

The structural resemblance of the various molecules referred to is graphically illustrated in Fig. 1. Inspection of these formulae shows that four operations would still be required for the conversion of N-methylmorphinan to morphine—namely, the introduction of a phenolic hydroxyl group, a secondary alcoholic hydroxyl group, an olefinic double bond and an oxygen bridge linking the aromatic with the hydrogenated ring. So far, only one of these operations has been successfully carried out—namely, the introduction of a phenolic hydroxyl group into the 3-position. Schnider and Grüssner, working at the research laboratories of Hoffmann LaRoche, Inc., Basle, Switzerland, synthesized 3-hydroxy-N-methylmorphinan (65)* as shown in Table II and later Schnider and Hellerbach (66a) prepared the compound as illustrated in Table IIa.

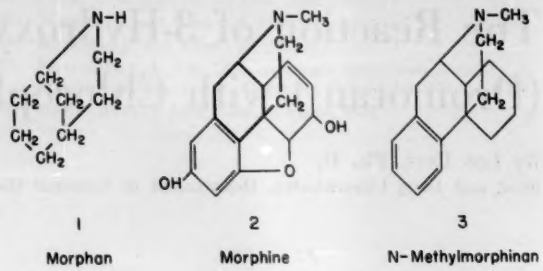


FIGURE 1

Structural formulae of morphan, morphine and N-methylmorphinan

The structural similarity of the hydroxylated derivative to morphine was soon found to be paralleled by striking similarities in pharmacological behaviour, the analgesic action of the compound proving equal and even superior to that of the natural opium alkaloid (3, 6, 10, 11, 15, 28, 29, 32, 39a, 41, 42, 43, 45, 47, 48, 50, 59, 63, 64, 67, 68, 70, 74, 78, 79, 81, 83). However, the extensive clinical evaluations also revealed that, like morphine, the compound—tentatively designated by Hoffmann LaRoche as NU-2206 (NU standing for Nutley, location of their U.S.A. headquarters, and 2206 being the laboratory number of the product) (66b)—was to be considered an addiction-producing drug. Single doses administered subcutaneously or intravenously produced euphoria and afforded relief of the withdrawal syndrome when given at the height of abstinence from morphine. Also, following abrupt withdrawal after prolonged administration definite signs of abstinence became apparent (28, 32, 45, 48, 63, 78, 79).

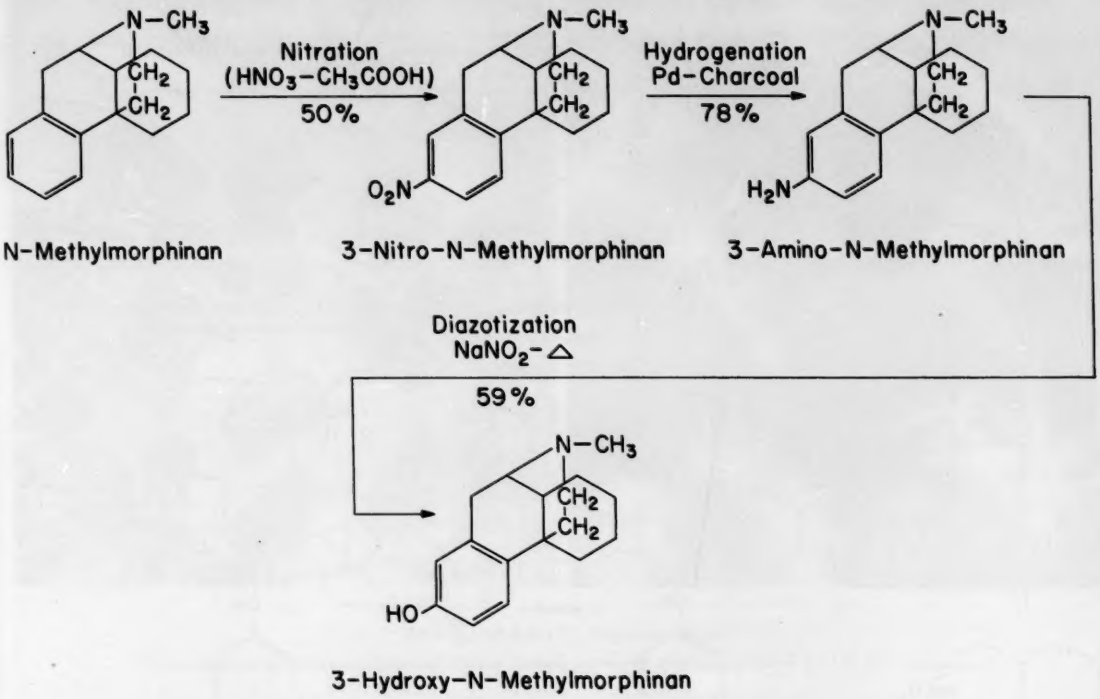
In the light of these findings the United States Government, pursuant to article I, paragraph 1, of the Paris Protocol, addressed on 17 October 1950 to the Secretary-General of the United Nations a notification, along with pertinent clinical reports from its Public Health Hospital at Lexington, Ky., stating that the drug which may be used for medical and scientific purposes was to be considered liable to the same kind of harmful effects as the drugs specified in article I, paragraph 2, of this Convention. The Secretary-General of the United Nations duly transmitted this communication to the other States Parties of the Protocol, the Commission on Narcotic Drugs and the World Health Organization, whose Expert Committee on Drugs Liable to Produce Addiction considered all relevant data at its third session held in Geneva, 7-12 January 1952. The Committee expressed the opinion " that 3-hydroxy-N-methylmorphinan, because it (1) produces morphine-like euphoria, (2) will suppress the abstinence phenomena of a known morphine addiction and (3) will sustain a morphine addiction, must be considered an

* Barltrop did not isolate the parent compound of this series, but only derivatives thereof. The unsubstituted, bicyclic secondary amine was synthesized two years later, independently and almost simultaneously, via lactamization of cis-3-aminocyclohexaneacetic acid and subsequent catalytic reduction of the resulting lactam, by Cronyn at the University of California, Berkeley, Cal. (14) and by Ginsburg at Rehovoth's Weizmann Institute of Science in Israel (31).

* Two other methods were reported by these workers at the same time.

TABLE II

Conversion of N-Methylmorphinan to 3-Hydroxy-N-Methylmorphinan according to Schnider and Grüssner



addiction-producing drug comparable to morphine" (79) and that, therefore, the regime laid down in the 1931 Convention for the drugs specified in article I, paragraph 2, group 1, should be applied to the synthetic alkaloid and its salts. The recommendation was referred back to the Secretary-General of the United Nations, who notified the States Parties accordingly. Thus, the drug 3-hydroxy-N-methylmorphinan came to be placed under international control.* It was marketed by Hoffmann LaRoche as the hydrobromide salt under the trade name of Dromoran®.

It should be emphasized at this point that chemically Dromoran was a racemoid (*d,l*-compound) and since such a substance is biologically always less active than either its *l*- or *d*-configuration (natural morphine is a levo isomer) further researches were carried out at the Hoffmann LaRoche laboratories to resolve the product into its optical antipodes. Schnider and Grüssner realized this process by treating the base with D-tartaric acid and separating the optically active salts on the basis of their different solubilities in water (66). Photomicrographs of the two isomers as published in Helvetica Chimica Acta are reproduced in Fig. 2.

Clinical evaluations soon showed that the dextro isomer exhibited no pain-relieving properties while the levo compound displayed considerably greater analgesic action than did the racemate (29, 45). Following these observations Hoffmann LaRoche discontinued manufacturing *d,l*-Dromoran Hydrobromide and began to market *l*-Dromoran Tartrate (Levo-Dromoran, Brand of Levorphan Tartrate) instead.

In Canada, Dromoran and Dromoran compounds were already included in the Schedule of the Opium and Narcotic Drug Act in 1950 (Order in Council PC 1578, dated 28 March 1950) by the Division of Narcotic Control acting in accordance with the international treaty known as the 1948 Paris Protocol.* Sensitive microchemical methods of identification and characterization thus became imperative and research along these lines was immediately begun in the federal laboratory.

* Provisionally, the compound had already been put under the regime laid down in the 1931 Convention for the drugs in group 1 following a resolution—taken in pursuance of article 2 of the Protocol—by the Commission on Narcotic Drugs, during its sixth session held in New York, 10 April-24 May 1951 (20).

* The nomenclature of these compounds may easily lead to confusion and it is here reproduced for reference purposes from a paper by Braenden and Wolff (5).

Levorphan*: (-)-3-hydroxy-N-methylmorphinan, also described as *l*-3-hydroxy-N-methylmorphinan
Synonyms: Dromoran, Laevo-Dromoran Tartrate

Racemorphan*: (±)-3-hydroxy-N-methylmorphinan, also described as rac. 3-hydroxy-N-methylmorphinan
Synonym: Cetarin (The name Dromoran was previously given to Racemorphan, but is now used for Levorphan).

Levomethorphan*: (-)-3-methoxy-N-methylmorphinan, also described as *l*-3-methoxy-N-methylmorphinan

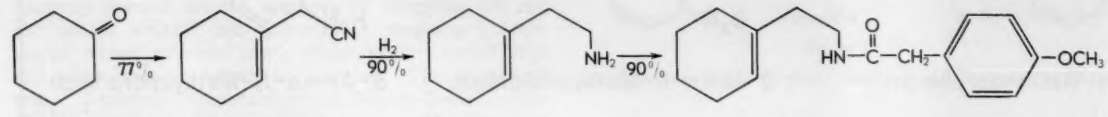
Racemethorphan*: (±)-3-methoxy-N-methylmorphinan, also described as rac. 3-methoxy-N-methylmorphinan

* Proposed International Non-proprietary Name

TABLE II a

Technical Synthesis of 3-Hydroxy-N-methylmorphinan according to Schnider and Hellerbach

Courtesy Schnider and Hellerbach (F. Hoffmann LaRoche & Co. Ltd., Basle, Switzerland)

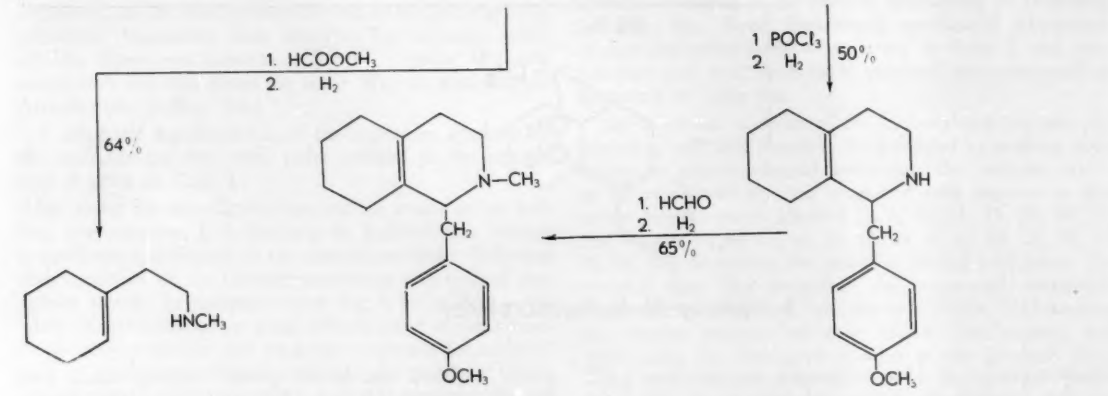


Cyclohexanone

1-Cyclohexene-1-acetonitrile

2-(1-Cyclohexene-1-yl)-ethylamine

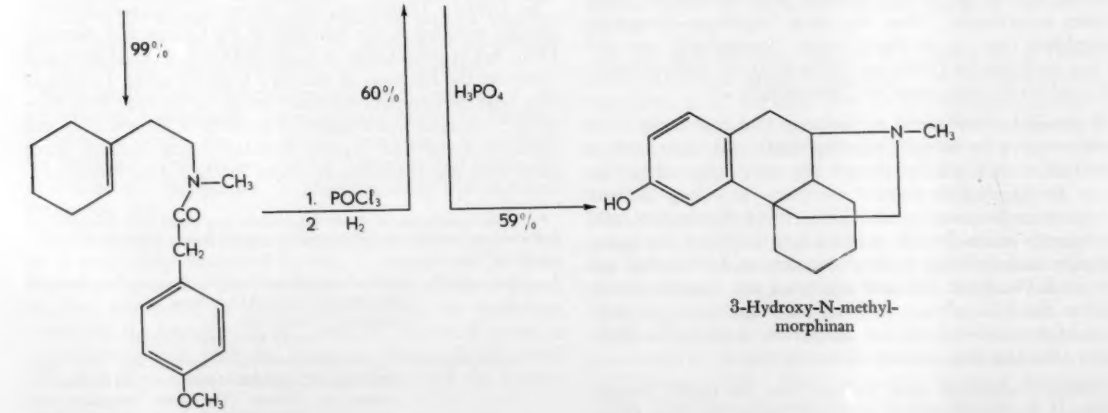
N-[2-(1-Cyclohexene-1-yl)-ethyl]-α-(p-methoxyphenyl)-acetamide



1-Methylamino-2-(1-cyclohexene-1-yl)-ethane

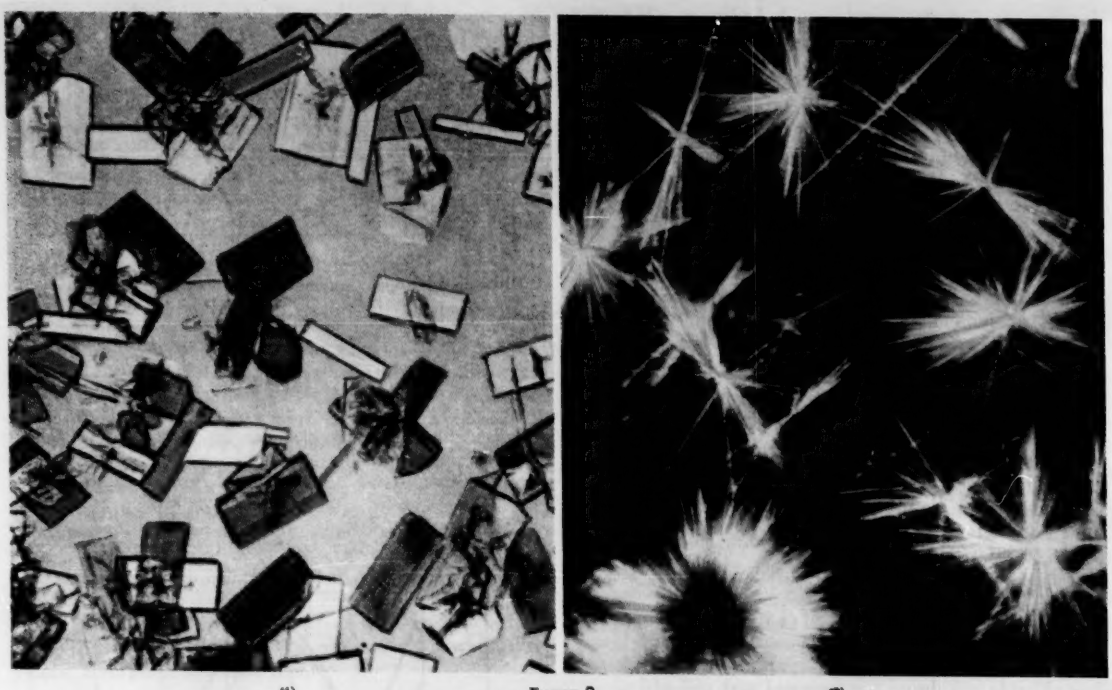
1-(p-Methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline

1-(p-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline



N-Methyl-N-[2-(1-cyclohexene-1-yl)-ethyl]-α-phenylacetamide

3-Hydroxy-N-methyl-morphinan



(1) FIGURE 2 (2)

Levo (1) *and dextro* (2) *Dromoran Tartrate*

Reproduced through the courtesy of Schnider and Grüssner, Research Laboratories, Hoffmann LaRoche & Co., Ltd., Basle (Switzerland) and the Editor of Helvetica Chimica Acta.

It soon became apparent that, unlike morphine, Dromoran was extremely reluctant to yield crystalline derivatives which would prove of value to the forensic chemist. Of 224 reagents tested, 222 gave amorphous precipitates and only two produced characteristic microcrystalline complexes suitable for the identification of minute amounts of the narcotic. These two reagents were Reinecke's Salt and chloroplatinic acid. The characterization of Dromoran (and other narcotics) with Reinecke's Salt has already been reported (54) and it is the purpose of this paper to present a study of the reaction of the clinically important drug with chloroplatinic acid.

EXPERIMENTAL RESULTS AND DISCUSSION

Preparation of the Derivative

To a solution of 0.005 moles (1.7365 g) of *d,l*-3-hydroxy-N-methylmorphinan hydrobromide in 150 ml of distilled water was added, slowly and with stirring, a solution of chloroplatinic acid, prepared by dissolving 0.005 moles of the salt (2.59 g of $H_2PtCl_6.6H_20$) in a mixture of 75 ml of 1 N hydrochloric acid and 75 ml of ethanol. The bulky, microcrystalline precipitate which formed gradually was filtered off after 12 hours, standing and dried *in vacuo* over phosphorous pentoxide. (Weight of product = 2.271 g or 98.24% theoretical yield.)

The yellowish-coloured compound—practically insoluble in water and organic solvents—was purified by reprecipitation with ethanol from 50 % aqueous acetone solution. Two such recrystallizations yielded a product, which after drying over P_2O_5 proved sufficiently pure for physico-chemical characterization.

Qualitative and Quantitative Analyses

The complex thus prepared could be dried at 100 °C. for two hours without suffering loss of weight or colour. Karl Fisher titrations showed that it did not contain any water of crystallization. It decomposed to a dark brownish liquid from 235-238 °C. as determined with a Fisher-Johns melting-point apparatus adjusted to a heating rate of 5 °C. per minute. When reacted with potassium iodide a brownish-red colouration was observed (platinum) (76), and on treatment with silver nitrate a flocculent precipitate formed immediately (halide ions). No colour formation was noted, however, when a sample was reacted with chlorine water in dilute sulphuric acid (absence of bromine) (76). Also, on addition of aqueous potassium chloride to a solution of the complex in dilute acetone a yellow precipitate formed almost immediately (presence of $PtCl_6^=$ ions) * (76), and on reaction with Froehde's reagent a dark blue-green colouration developed immediately (3-hydroxy-N-methylmorphinan) (21).

Quantitative analyses indicated that the composition of the complex was in agreement with the formula $[C_{17}H_{23}NO.H]_2.[PtCl_6]$. The alkaloid and metal were determined following

* $PtCl_4$ gives no precipitate with potassium salts—or at least only after long standing (76).

decomposition of the complex with hydrogen sulfide and the halide was estimated as silver chloride.

Determination of the Metal

About 0.1 g of the derivative was weighed out accurately and dissolved with gentle heat in 100 ml of 2% aqueous hydrochloric acid. A slow stream of hydrogen sulfide was passed through the hot solution and the precipitated platinum sulfide—filtered off after 12 hours' standing—ignited to constant weight in a muffle furnace.

Determination of the Narcotic

The filtrate collected from the previous assay was evaporated to a volume of about 20 ml, made alkaline with dilute sodium carbonate solution and extracted with successive 20-ml portions of chloroform. Removal of the alkaloid from the aqueous system was considered complete when the residue obtained after evaporation of five drops of the organic layer did no longer respond to Fulton's phosphomolybdic acid test (30). After washing twice with 3-ml portions of distilled water the extract was placed on a steam bath and following removal of the solvent dried at 100°C. The residue was weighed as 3-hydroxy-N-methylmorphinan (M.P. 248-251°C.).

Determination of the Halide

Like morphine, Dromoran and Dromoran compounds were found to reduce silver salts to metallic silver and hence when reacting the complex with silver nitrate the precipitated silver chloride was always contaminated with colloidal silver. It was found possible to remove the metal from the system via conversion to silver sulphide and subsequent decomposition of the silver salt by means of nitric acid.

About 100 mg of the finely powdered complex were weighed out accurately into a 100-ml beaker. An equal quantity of sodium sulphide was added and the mixture triturated intimately with 5 ml of distilled water. During this operation black platinum sulphide precipitated while the liberated halide was converted to sodium chloride. After diluting to a volume of about 50 ml, the preparation was placed on a steam bath for half an hour to insure completion of the reaction and, following replacement of the water lost by evaporation, acidified with 5 ml of 10% sulphuric acid in order to convert all excess sodium sulphide to hydrogen sulphide. The precipitated platinum sulphide was filtered off—along with some colloidal sulphur which formed on standing—and to the filtrate was added a solution of 0.3 g of silver nitrate in 25 ml of water containing 1 ml of nitric acid. After 12 hours the supernatant liquid was decanted through a Whatman No. 42 filter paper and, using about 10 ml of water, any precipitate carried over was carefully transferred back to the bulk of the residue. Three ml of concentrated nitric acid were added to it and the suspension was digested on a steam bath for about 15 minutes in order to convert all silver sulphide contaminating the silver chloride to soluble silver nitrate.

$$3\,Ag_2S + 8\,HNO_3 \rightleftharpoons 6\,AgNO_3 + 2NO + 4H_2O + 3S$$

After diluting with 75 ml of distilled water the mixture was placed in the dark overnight, the silver chloride filtered off in subdued light, washed with a little ethanol and carbon disulphide to remove free sulphur (see equation), dried at 110°C. and weighed. The experimental data are recorded in Table III.

TABLE III

Composition of Dromoran-platinic Chloride Complex (%)

$[Dromoran\cdot H]_2\cdot[PtCl_6]$; M.W. = 924.71

Platinum		*Dromoran*		*Chlorine*	
Found	*Theory*	*Found*	*Theory*	*Found*	*Theory*
21.03	21.10	55.09	55.67	22.79	23.00
20.84		55.38		22.36	

Physicochemical Characterization of the Derivative

Ultraviolet Absorption

A 0.00002974-molar aqueous solution of the complex was prepared (0.0275 g dissolved with gentle heat in 1000 ml of distilled water) and its ultraviolet absorption measured in a Beckman Model DU Spectrophotometer equipped with photomultiplier tube. Similar determinations were made on

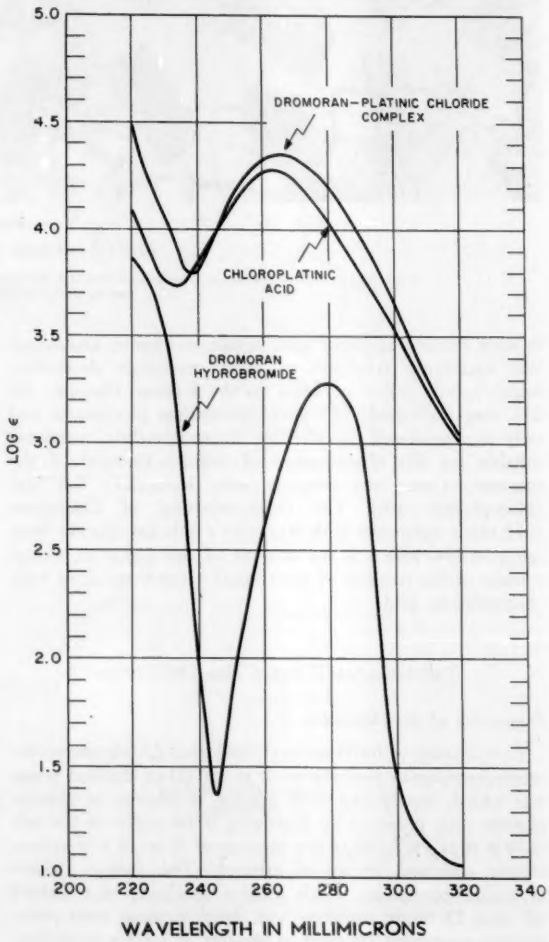


FIGURE 3

Ultraviolet absorption spectra of Dromoran Hydrobromide, Dromoran platinic chloride and chloroplatinic acid

TABLE IV

Characteristic UV-spectral Data for Dromoran Hydrobromide, Dromoran Platinic Chloride and Chloroplatinic Acid

Compound	Concentration (g/l)	max. (mμ)	εmax.	min. (mμ)	εmin.
Dromoran hydrobromide .	0.1051	279	1,881	245	23.4
Dromoran platinic chloride	0.0275	265	22,126	238	6,321
Chloroplatinic acid.....	0.0172	262	19,117	232	5,649

the alkaloidal salt and the inorganic reagent. The experimental data are recorded in Fig. 3 and Table IV.

Because of the deliquescent nature of chloroplatinic acid, its ultraviolet absorption could not be measured directly on accurately weighed samples of the compound. Good results were obtained, however, by analysing, prior to UV-determinations, 50-ml aliquots of an approximately 0.0025-molar aqueous solution of the salt for platinum (precipitation by means of hydrogen sulphide) and chlorine (precipitation by means of silver nitrate). Duplicate determinations showed the presence of 20.55 mg of platinum or the equivalent of 43.19 mg of anhydrous chloroplatinic acid and 22.21 mg of chlorine or the equivalent of 42.80 mg of anhydrous chloroplatinic acid per sample. The solution was therefore considered to contain 0.8599 g of anhydrous H_2PtCl_6 per litre. Ten ml of this preparation were diluted to 500 ml with distilled water to make a 0.00005-molar solution whose ultraviolet absorption was measured.

Comparison of the spectral curves reproduced in Fig. 3 shows that the complex exhibits an absorption pattern considerably different from that of the alkaloidal salt used for its synthesis, which observation indicates that formation of the derivative may be used advantageously for the characterization of the narcotic. One can also see that the inorganic salt, by virtue of the fact that it absorbs strongly in the ultraviolet region and comprises 44.34% by weight of the compound, affords a decisive contribution to the ultraviolet absorption characteristics of the complex. It should further be noted—see Table IV—that the molar extinction coefficient of the complex exceeds the sum values of the molar absorptions exhibited by the alkaloidal salt and the reagent. Evidently, the process of complex formation is associated with considerable electronic exaltation of the molecular system.

Further ultraviolet data were assembled by isolating the narcotic from the complex in accordance with the procedure described and measuring its absorption at two different pH values. The experimental results are recorded in Figs 4 and 5 and characteristic constants of the compound listed in Table V along with similar data on the methylated analogue, 3-methoxy-N-methylmorphinan, and the closely related opium alkaloids morphine and codeine.

The narcotics dissolved readily in buffer systems at pH 4 and both morphine and codeine solubilized without difficulty at pH 11. Dromoran and Methoxydromoran, however, were found to be practically insoluble in aqueous alkaline media and their UV-absorptions were measured by first

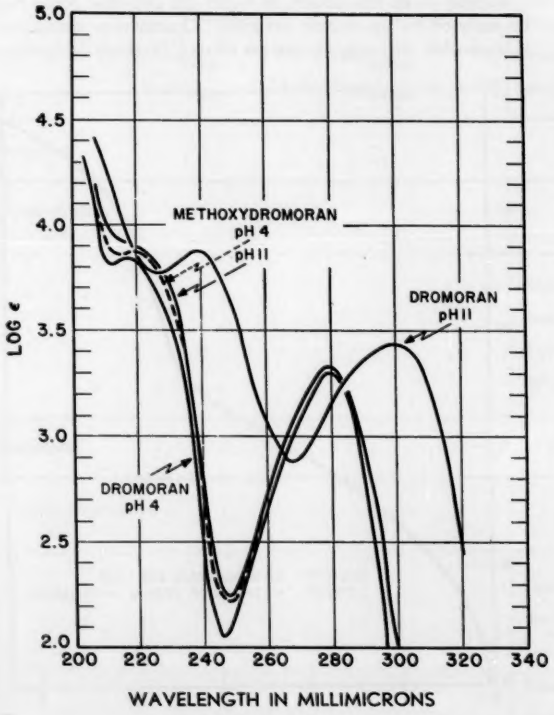


FIGURE 4

Ultraviolet absorption of dromoran and methoxydromoran at different pH-values

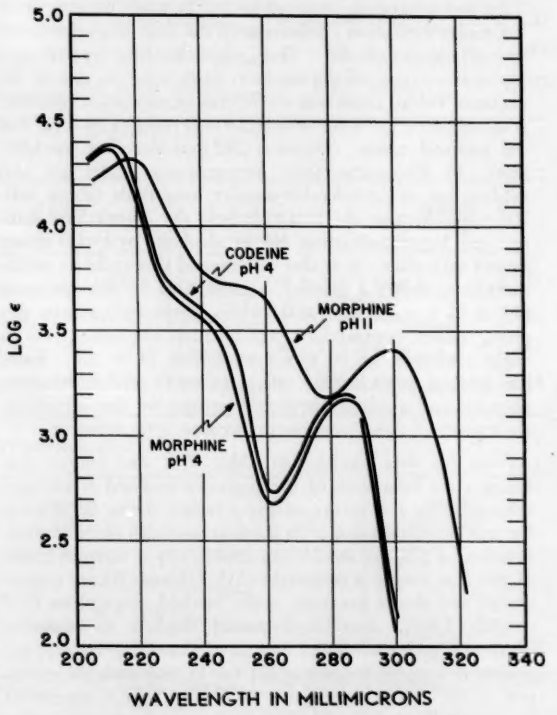


FIGURE 5

Influence of pH on ultraviolet absorption of morphine and codeine

dissolving representative samples in 5 ml of ethanol. The buffer systems employed were those described by Morgan (57) and they also served as blanks in all of the measurements reported.

It can be seen that at a pH of 4 Dromoran exhibits two maxima (218 and 279 mμ) both of which are displaced by 21 mμ toward higher wavelengths at pH 11 and similar bathochromic shifts move its minima, occurring at 212 and 246 mμ, to 226 and 267 mμ, respectively. Morphine also displays such pH-dependence of its ultraviolet absorption, the maxima occurring at 210 and 286 mμ as well as the minimum observed at 262 mμ shifting progressively toward higher wavelengths (by 8, 12 and 17 mμ respectively) as the pH of the system is increased from 4 to 11. Codeine (methylated morphine) does not show this phenomenon and, likewise, Methoxydromoran (3-methoxy-N-methylmorphinan) displays neither hypso- nor bathochromic absorption shifts with change in pH. Evidently, the phenolic hydroxyl group present in Dromoran and morphine (production of phenolate ions) is responsible for this characteristic ultraviolet behaviour pattern. It should also be noted that one of the maxima (216 mμ) and one of the minima (220 mμ) exhibited by Methoxydromoran at pH 4 are no longer detectable at pH 11. These bands are to be considered characteristic of the ionic species of the alkaloid. They disappear at higher pH values when dissociation of the base is suppressed and only molecular absorption takes place. No such phenomenon is shown by codeine because this compound may ionize in both acidic and basic media (presence of alcoholic hydroxyl group).

Further interesting observations can be made by comparing the molar extinction coefficients of the four narcotics at the two pH values recorded. Thus, when changing the hydrogen ion concentration of the medium from 4 to 11, one of the maximal molar extinction coefficients of morphine (286 mμ) is increased by 1,036, the other (210 mμ) reduced by 2,747 and the minimal molar extinction (262 mμ) increased by 1,099 units. In Dromoran these hyperchromic shifts are also evident but of considerably smaller magnitude (about 600-700 units) because the molecule lacks the 7,8-ethylenic linkage and hyperconjugation via an alcoholic hydroxyl group cannot take place. It is also to be noted that codeine, unlike morphine, shows a general depression of its absorption at pH 11 ($\Delta\varepsilon = -6$ to -454), while Methoxydromoran displays, under comparable experimental conditions, but a slight exaltation of its molar extinction (8 to 28). Thus, the marked auxochromic effects of methoxyl substituents, phenolic and alcoholic hydroxyl groups on the ultraviolet absorption of these compounds become very apparent.

From the data recorded in Table V it also follows that the spectral behaviour of the narcotics analysed is strongly influenced by the nature of the solvent. Thus, in ethanol, Dromoran exhibits one of its maxima and both of its minima, observed at 279, 212 and 246 mμ respectively in aqueous media of pH 4, at longer wavelengths (283, 218 and 251 mμ respectively) and shows generally more marked absorptions ($\Delta\varepsilon = 100 - 2{,}658$). Methoxydromoran displays in ethanol a maximum and a minimum (289 and 287 mμ respectively) not present in aqueous systems at pH 4 or 11, and with the exception of its minimal absorption at 248 mμ, which appears to be practically independent of pH and solvent, its molar extinction is generally also higher in ethanol ($\Delta\varepsilon = 244 - 521$) than in aqueous media. These UV characteristics are less pronounced in the spectra of morphine and codeine, which compounds exhibit both their maxima and minima at practically identical positions and show comparable molar extinctions in both ethanol and slightly acidic media. The only conspicuous feature to be noted is the absence of a maximum in the ethanol spectrum of morphine at 210 mμ where marked absorption occurs when the compound is examined in aqueous systems at pH 4 and 11.

The phenomena observed are not readily explained and a considerable amount of fundamental investigations into the effects of hydrogen bonding, temperature, conjugation and dipole moment on the spectra of these compounds and their analogues would have to be done before providing even tentative interpretations. Unfortunately no systematic collection of data of this kind nor of the type here reported is at present available for narcotics and related alkaloids. It would, no doubt, prove of great practical value to the forensic chemist because such data form the basis of sensitive differential methods of analysis, yield a considerable amount of information regarding the chemical constitution of narcotic compounds and are of cardinal importance for elucidating the mechanisms of their reactions (4, 7, 8, 9, 12, 13, 16, 17, 18, 19, 22, 23, 23a, 24, 25, 26, 27, 33, 34, 36, 37, 44, 46, 49, 51, 52, 53, 55, 56, 57, 58, 60, 61, 62, 69, 71, 72, 73, 75, 77, 82). It is contemplated to carry out such research at the federal laboratory and publish a survey of this nature as continuation of the work of Oestreicher, Farmilo and Levi comprising the ultraviolet spectra of narcotics and related compounds (61).

Potentiometric Titration

Because of its insolubility in water the complex could not be analysed by aquametric titration. Quantitative estimation was possible, however, by means of 0.05 N alcoholic sodium

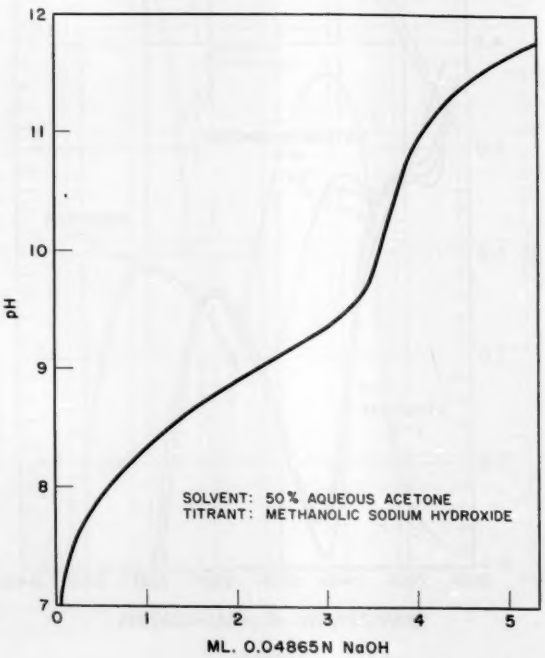


FIGURE 6

Electrometric titration of Dromoran-Platinic Chloride Complex

TABLE V

Effect of Solvent and pH on Ultraviolet Absorption of Morphine, Codeine, Dromoran and Methoxydromoran

Author	*Clark and McBay**		*Oestreicher, Farmilo and Levi*	*Levi and Beaudry*	
Compound	MORPHINE				
Solvent	Dilute sulphuric acid	Dilute sodium hydroxide	Ethanol	Aqueous buffer solutions (57)	
pH	4	12	—	4	11
	Absorption maxima, minima and molar extinction coefficients				
Concentration (g/l)	0.1000	0.1000	0.1046	0.01016 0.10160	0.00820 0.08200
	————	————	————	$\varepsilon max_{210m\mu}$ = 23,156	$\varepsilon max_{218m\mu}$ = 20,409
	$\varepsilon min_{262m\mu}$ = 468	$\varepsilon min_{280m\mu}$ = 1,555	$\varepsilon min_{263m\mu}$ = 465	$\varepsilon min_{262m\mu}$ = 458	$\varepsilon min_{279m\mu}$ = 1,557
	$\varepsilon max_{286m\mu}$ = 1,509	$\varepsilon max_{298m\mu}$ = 2,545	$\varepsilon max_{287m\mu}$ = 1,510	$\varepsilon max_{286m\mu}$ = 1,516	$\varepsilon max_{298m\mu}$ = 2,544
Compound	CODEINE				
Concentration (g/l)	0.1000	0.1000	0.01072 0.10720	0.01024 0.10240	0.01080 0.10800
	————	————	$\varepsilon max_{211-212m\mu}$ = 24,000	$\varepsilon max_{212m\mu}$ = 24,264	$\varepsilon max_{212m\mu}$ = 23,810
	$\varepsilon min_{262m\mu}$ = 551	$\varepsilon min_{262m\mu}$ = 560	$\varepsilon min_{263m\mu}$ = 535	$\varepsilon min_{261m\mu}$ = 555	$\varepsilon min_{261m\mu}$ = 549
	$\varepsilon max_{284m\mu}$ = 1,611	$\varepsilon max_{284m\mu}$ = 1,488	$\varepsilon max_{286m\mu}$ = 1,550	$\varepsilon max_{284m\mu}$ = 1,605	$\varepsilon max_{284m\mu}$ = 1,480
Compound	DROMORAN				
Concentration (g/l)			0.0109 0.0544	0.00992 0.05089 0.21052	0.00584 0.06375
	————		$\varepsilon min_{218m\mu}$ = 9,200	$\varepsilon min_{212m\mu}$ = 6,542	$\varepsilon min_{226m\mu}$ = 6,037
			$\varepsilon max_{219m\mu}$ = 9,000	$\varepsilon max_{218m\mu}$ = 6,735	$\varepsilon max_{239m\mu}$ = 7,492
			$\varepsilon min_{251m\mu}$ = 212	$\varepsilon min_{246m\mu}$ = 112	$\varepsilon min_{267m\mu}$ = 727
			$\varepsilon max_{283m\mu}$ = 2,350	$\varepsilon max_{279m\mu}$ = 1,986	$\varepsilon max_{300m\mu}$ = 2,644
Compound	METHOXYDROMORAN				
Concentration (g/l)			0.02060 0.10320	0.01148 0.1756 0.4121	0.00964 0.07560
	————		$\varepsilon min_{218m\mu}$ = 7,420	$\varepsilon min_{216m\mu}$ = 6,899	————
			$\varepsilon max_{220-221m\mu}$ = 7,510	$\varepsilon max_{220m\mu}$ = 7,202	————
			$\varepsilon min_{248m\mu}$ = 158	$\varepsilon min_{248m\mu}$ = 162	$\varepsilon min_{248m\mu}$ = 170
			$\varepsilon max_{281m\mu}$ = 2,320	$\varepsilon max_{278m\mu}$ = 2,076	$\varepsilon max_{278m\mu}$ = 2,104
			$\varepsilon min_{287m\mu}$ = 2,050	————	————
			$\varepsilon max_{289m\mu}$ = 2,110	————	————

* The molar extinction coefficients reported for morphine and codeine were calculated from the optical density data determined by these authors (13).

hydroxide, in a solvent system consisting of equal parts of water and acetone. Two moles of titrant were found to be consumed per mole of complex in accordance with the equation:

$$[\text{Dromoran}\cdot\text{H}]_2\cdot[\text{PtCl}_6] + 2\ \text{NaOH} \longrightarrow 2\ \text{Dromoran}\cdot\text{H}^+ + 2\ \text{OH}^- + \text{Na}_2\text{PtCl}_6.$$

The titration curve showed a sharp break at the equivalence point—see Fig 6—and indicated a recovery of 99.87%. Also from the experimental data a dissociation constant (pK_B^1) of 5.68 was calculated for the narcotic. This value agrees closely with that derived by Levi and Farmilo by analysis of the Dromoran-Reineckate complex (54).

Infrared Absorption

Infrared absorption spectra of the complex along with those of the narcotic-free base and its hydrobromide salt were obtained by the mineral oil mull and the pressed potassium bromide pellet technique. They were charted on a linear frequency Perkin Elmer Model 21 Double Beam Recording Spectrophotometer, calibrated against atmospheric water-vapour and operated under the following conditions: slit auto; resolution 927; gain 5.9; response 1; source amperes 0.3; speed 3; suppression 0. The estimated errors in the frequencies reported are ± 5 cm^{-1} throughout the 4000-2000 cm^{-1} region and ± 2 cm^{-1} beyond this wavelength range.

The mineral oil (Nujol) spectra were obtained by grinding finely with an electric vibrator a few mg of sample in the vehicle, placing the resultant smooth paste between two salt plates and measuring its absorption throughout the 4000-650 cm^{-1} frequency range. A sodium chloride window was used in the reference beam during the experiments.

The KBr spectra were obtained by first powdering the specimens finely in a mechanical grinder until they would pass through a 250-mesh sieve (U.S. Standard Sieve Series No. 230). About 2 mg of sample were then mixed intimately with 400 mg of A.C.S. Reagent Grade potassium bromide prepared similarly and dried overnight at 125 °C. A 200-mg aliquot of the mixture was subject *in vacuo* for about five minutes to a pressure of 10,000 lbs/sq. inch and the absorbance of the resulting clear disc recorded. A KBr window prepared under comparable conditions was placed in the path of the reference beam to compensate for absorption by the reagent.

Examination of the spectra reproduced in Figs. 7 and 8 shows that in marked contrast to the few (4-6) bands displayed in the ultraviolet, the compounds exhibit a great number of characteristic absorptions in the infrared. Furthermore, whereas all UV-characteristics of the narcotic (and its hydrobromide salt) are modified as a result of complex formation —see Fig. 3—many of its prominent features are retained in the infrared. This special UV-IR interrelationship has inherent advantages and demonstrates the complementary nature of the two techniques.

Thus, in Nujol both the narcotic-free base and the complex show two intense bands (1618 cm^{-1} and 1578 cm^{-1}) none of which is present in the spectrum of the alkaloidal salt. Additional key bands appearing in the mineral oil spectra of the compounds are listed in Table VI. Similar common characteristics as well as differentiating features are observed in the KBr-spectra shown in Fig. 8. A more detailed interpretation of their significance in terms of structure is to make the subject of another paper supplementing the Atlas of Infrared Spectra of Narcotics and Related Alkaloids published by Levi, Hubley and Hinge (52a).

TABLE VI

Key Bands in Nujol Spectra of Dromoran, Dromoram Hydrobromide and Dromoran Platinic Chloride

Characteristic IR-absorptions (cm^{-1})	*Compounds*		
	Dromoran	*Dromoran· HBr*	*[Dromoran·H]₂·[PtCl₆]*
3520	—	weak	strong
3265	—	strong	—
3225	—	—	strong
3100	—	—	strong
2700	—	strong	—
1618	strong	—	strong
1607	—	strong	—
1578	strong	—	strong
1505	—	weak	—
1495	—	—	strong
1490	—	weak	—
1375	strong	strong	strong
1280	strong	strong	strong
1240	strong	weak	strong
1170	medium	strong	medium
1160	medium	—	weak
1115	medium	weak	strong
1095	medium	strong	—
1090	—	—	strong
1050	strong	weak	strong
1000	strong	—	—
910	weak	medium	medium
885	strong	strong	strong
865	—	strong	strong
860	strong	—	—
850	weak	strong	weak
820	—	strong	—
810	—	—	strong
800	strong	—	—
760	strong	—	weak
730	medium	—	—
725	—	strong	strong
700	—	weak	medium
695	medium	—	—

Mechanism of the Reaction

The analytical data reported strongly suggest that the derivative is formed via interaction of the $PtCl_6^{=}$ ion, supplied by the reagent, with the alkaloidal cation, produced as a result of the virtually complete ionization of the salt in water.

1. $H_2PtCl_6 \rightleftharpoons 2\ H^+ + PtCl_6^{=}$
2. $\text{Dromoran}\cdot\text{HBr} \rightleftharpoons \text{Dromoran}\cdot\text{H}^+ + \text{Br}^-$
3. $2\ \text{Dromoran}\cdot\text{H}^+ + PtCl_6^{=} \rightleftharpoons [\text{Dromoran}\cdot\text{H}]_2\cdot[PtCl_6]$

Further support for this mechanism of complex formation stems from the following experimental observations.

1. *d,l*-3-hydroxy-N-methylmorphinan (0.5 g) was dissolved in a solution of 50 ml of 1 N hydrochloric acid and 50 ml of ethanol. To this system was added slowly and with constant stirring a solution of 1 g of chloroplatinic acid in 50 ml of aqueous ethanol (1:1). The reaction product, isolated and purified in accordance with the procedure previously described, proved to be identical with that obtained when *d,l*-3-hydroxy-N-methylmorphinan hydrobromide was used as reactant.

2. *d,l*-3-hydroxy-N-methylmorphinan (0.5 g) was dissolved in 100 ml of 90% aqueous ethanol and to this solution were added slowly and with stirring 50 ml of an ethanolic 0.5% chloroplatinic acid solution. After refrigeration overnight the yellow precipitate was filtered off—because of the colloidal nature of the product this process was very slow—and dried *in vacuo*. Only 0.16 g of material was isolated which, after purification, proved to be identical with the preparation obtained by the previous method.

The decreased sensitivity of the process observed under these conditions is in accord with the proposed mechanism of the reaction. The alkaloidal base ionizes only partially in the solvent system used,

d,l-3-hydroxy-N-methylmorphinan + $H_2O \rightleftharpoons$ *d,l*-3-hydroxy-N-methylmorphinan·H^+ + OH^-

hence the supply of cations is depressed and the reaction proceeds more sluggishly.

3. The reaction was carried out in dilute half-normal hydrobromic acid instead of half-normal hydrochloric acid. Again the product obtained showed the composition [Dromoran·H]$_2$·[$PtCl_6$]. All attempts to prepare a complex containing both bromine and chlorine ions—e.g., [Dromoran·HBr]$_2$·[$PtCl]_4$ or [Dromoran·HCl]$_2$·[$PtBr_4$] failed. These observations further support the suggested mechanism of the reaction in so far as they are in full accord with all the analytical data favouring the formula [Dromoran·H]$_2$·[$PtCl_6$] —rather than [Dromoran·HCl]$_2$·[$PtCl_4$]—for the isolated complex.

4. It was possible, however, to prepare the fully brominated compound by reacting the narcotic with platinic bromide in accordance with the following procedure. To a

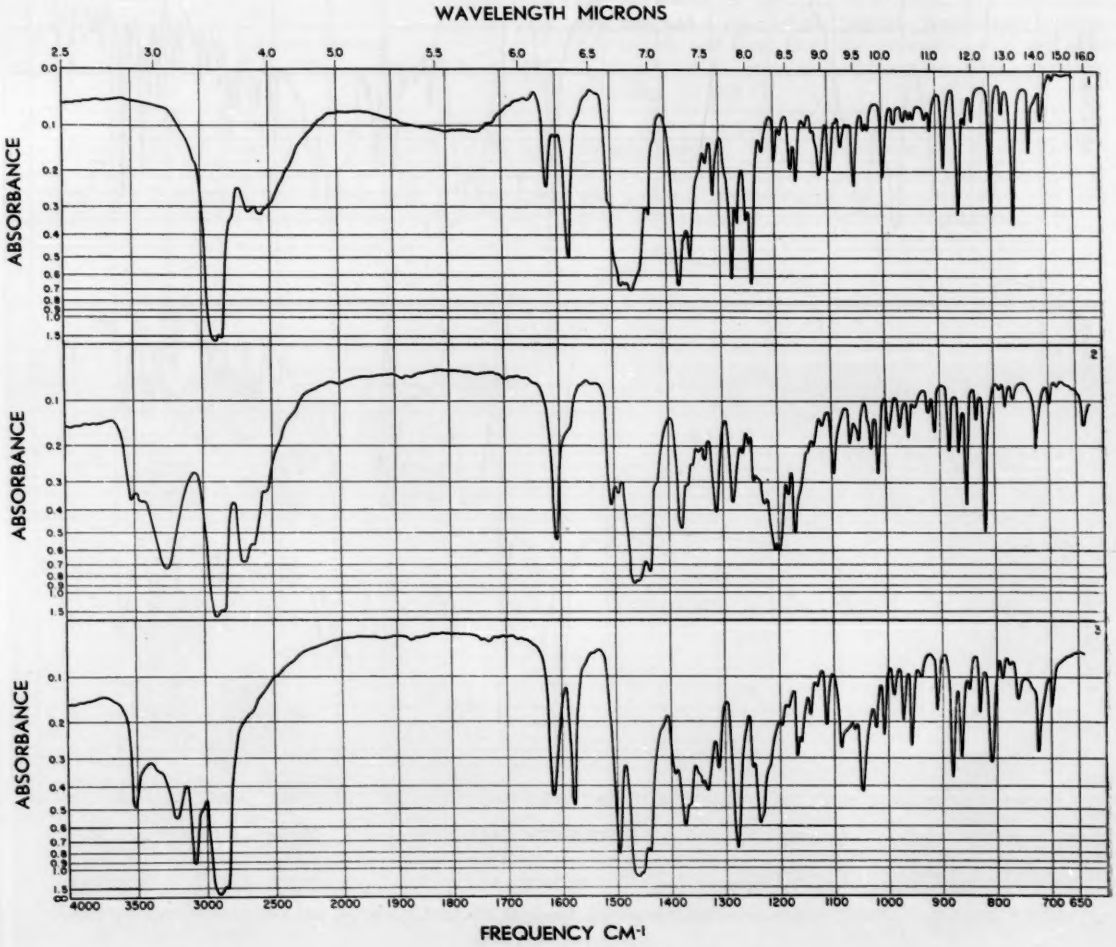


FIGURE 7

Infrared spectra of Dromoran (1), *Dromoran Hydrobromide* (2) *and Dromoran Platinic Chloride* (3) (*Mineral oil mulls*)

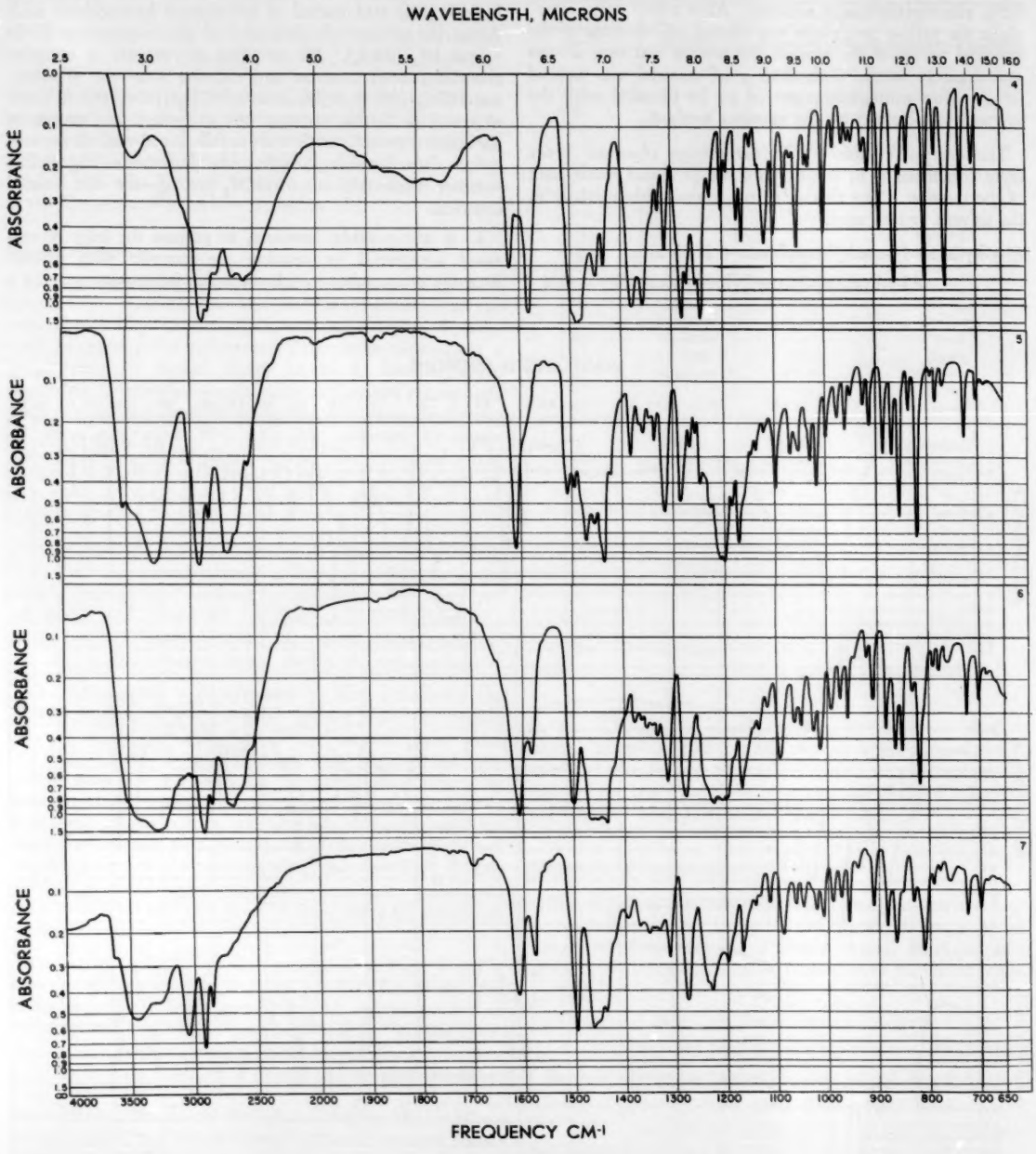
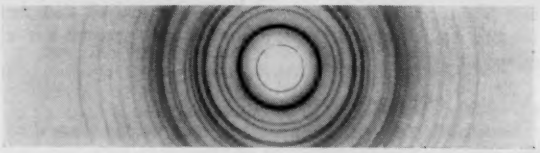


FIGURE 8

Infrared spectra of Dromoran (4), Dromoran Hydrobromide (5), Dromoran Platinic Chloride (6) and Dromoran Platinic Bromide (7) in potassium bromide



(1) *Dromoran Platinic Chloride*

(2) *Dromoran Platinic Bromide*

FIGURE 9

X-Ray Diffraction Pattern of Dromoran Platinic Chloride (1) *and Dromoran Platinic Bromide* (2)

solution of 0.5209 g of *d,l*-3-hydroxy-N-methylmorphinan hydrobromide (0.0015 moles) in 50 ml of distilled water was added a solution of 0.7723 g of platinic bromide (0.0015 moles) in 50 ml of 1 N ethanolic hydrobromic acid. The precipitated complex was filtered off and dried over P_2O_5. (Weight of product = 0.860 g or 96.4% Theoretical Yield.) It was of a deep orange colour and following purification melted with decomposition from 249-253 °C. Quantitative analyses carried out in accordance with the procedure described earlier showed that it had the composition $[Dromoran \cdot H]_2 \cdot [PtBr_6]$. (Pt found: 16.04 %; Theoretical 16.37 %; Br found: 39.91% Theoretical 40.23%; Dromoran found: 42.69%; Theoretical 43.18%.) Its X-ray diffraction pattern is shown in Fig. 9 and its infrared absorption recorded in Figs. 7 and 8.

Microchemical Value of the Reaction

Under suitable conditions the reaction described becomes highly sensitive and may be used for the identification of trace amounts of the narcotic. The technique to be adopted for this purpose is as follows:

Weigh out 0.250 g of chloroplatinic acid and dissolve in 100 ml of 50% ethanolic half-normal hydrochloric acid. Place a little of the specimen to be tested on a microscope slide and add a drop of the reagent. Immediately rosette-like crystals will form from the amorphous mass and start floating in all directions toward the edges of the test drop —see Figs. 10 and 11.

The reaction is particularly sensitive when carried out on the solid material. Hence, if a solution is to be analysed it is best to evaporate a drop of it to dryness on a microscope slide and perform the test directly on the residue. As little as 1 γ of the narcotic may thus be readily detected.

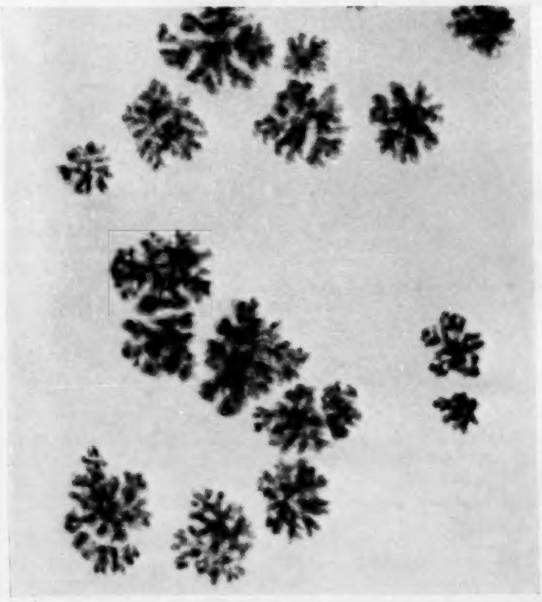


FIGURE 10

Crystals of Dromoran with platinic chloride observed after 5 seconds

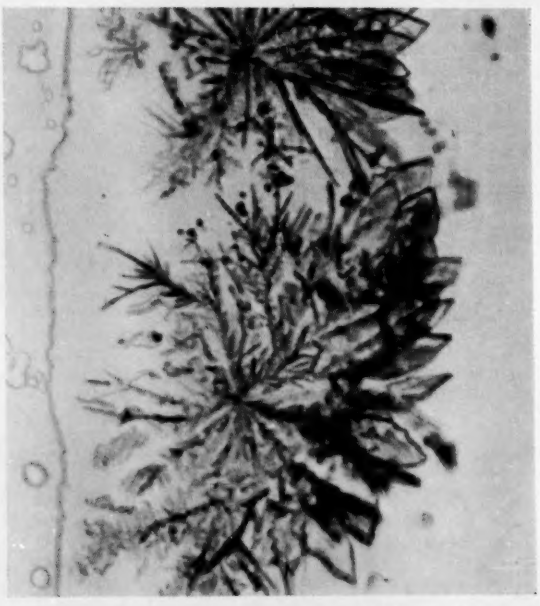


FIGURE 11

Crystals of Dromoran with platinic chloride observed after 1 minute

The sensitivity of the microchemical reaction described is matched by a high degree of specificity. No characteristic crystalline derivatives are obtained with morphine and morphine salts, ethylmorphine, dihydromorphine, dihydromorphinone, heroin hydrochloride, codeine phosphate, dihydrocodeine, dihydrocodeinone, metopon, thebaine, narcotine, Phenadoxone and Demerol. All of these drugs, with the exception of heroin hydrochloride, dissolve on addition of the reagent and only after evaporation of the ethanol from the slide will some of them start to crystallize from the medium. The reagent therefore exceeds by far the sensitivity and specificity of Reinecke's Salt, which yields microcrystalline derivatives with the opium alkaloids as well (54).

It should be pointed out, however, that the sensitivity of the test is not the same for all Dromoran compounds. The free base reacts somewhat more sluggishly than the hydrobromide salt and the tartrate is even less reactive than the free base. These observations further confirm the reaction mechanism described earlier, and accordingly the phenomenon may be overcome by adding to the sample on the microscope slide a drop of hydrochloric acid, evaporating the solution to dryness and performing the test on the residual salt.

The reagent may also be used for the microchemical identification of *d*- and *l*-3-methoxy-N-methylmorphinan ★—see Fig. 12—as well as of the *d,l*-isomer—see Fig 13. The observation that the latter compound yields different crystals than its optical antipodes is in line with the finding of Barnes and Sheppard (2), who showed by X-ray analysis that the narcotic is not a mixture of two isomers but represents a true racemoid.

★ Only *l*-3-methoxy-N-methylmorphinan is considered a narcotic. The *d*-isomer lacks analgesic properties (45, 80).

Additional Microchemical Identification Tests

Since this work was completed, several papers relating to the microchemical identification of Dromoran have appeared in the literature. Reference to these researches is made in a special section of the bibliography cited at the end of this article, so as to enable the forensic chemist and toxicologist to locate pertinent data more readily. Also, in private correspondence with Dr. Goldbaum, Chief, Division of Physiology and Pharmacology, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D.C., the author was told of a sensitive chromatographic method of alkaloid analysis applicable to Dromoran. Those interested in experimental details are advised to communicate with Dr. Goldbaum directly (35).

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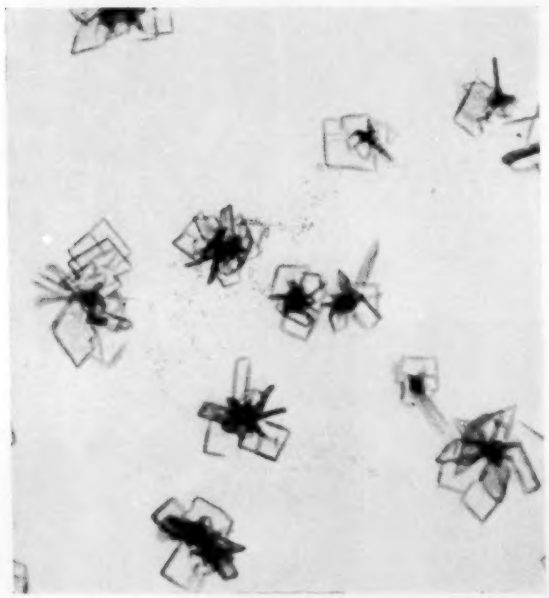

FIGURE 12

Crystals of d *or* l-*Methoxydromoran with platinic chloride*

FIGURE 13

Crystals of d,l-*Methoxydromoran with platinic chloride*

LITERATURE CITED

1. BARLTROP, J. A., " Syntheses in the Morphine Series. Part. I. Derivatives of Bicyclo-(3, 3, 1)-2-Azanonane ", *Jour. Chem. Soc.*, 399 (1947).
2. BARNES, W. H., and SHEPPARD, H. M., " X-Ray Diffraction Powder Data for eighty three Narcotics ", *Bull. Narcotics, 6* (2), (1954).
3. BECKER, J., and BUNDSCHUH, O., *Med. Klinik, 47*, 546 (1952).
4. BRACKETT, J. W., and BRADFORD, L. W., " Detection, Identification and Estimation of Non-volatile Organic Poisons, Drugs and Narcotics by Ultraviolet Spectrophotometry ". Paper presented at 123rd Meeting of the American Academy of Forensic Sciences, Los Angeles, Cal., March 1953.
5. BRAENDEN, O. J., and WOLFF, P. O., " Synthetic substances with Morphine-Like Effect ", *Bull. World Health Org., 10*, 1003 (1954).
6. BRAENDEN, O. J., EDDY, N. B., and HALBACH, H., " Synthetic Substances with Morphine-Like Effect. Relationship between Chemical Structure and Analgesic Action ". United Nations Economic and Social Council publication, E/CN 7/299, 30 March 1955.
7. BRAND, J. C. D., HORNING, W. C., and THORNLEY, M. B., " The Spectrophotometric Determination of the Ionization Constants of Aromatic Nitro-Compounds ", *Jour. Chem. Soc.*, 1374 (1952).
8. BRAND, J. C. D., " Aromatic Sulphonation. The Ionization Constants of p-Nitrotoluene, Nitrobenzene and p-Chloronitrobenzene and the Acidity Function of Oleum ", *Jour. Chem. Soc.*, 997 (1950).
9. BRODE, W. R., " The Determination of Hydrogen Ion Concentration by a Spectrophotometric Method and the Absorption Spectra of Indicators ", *Jour. Amer. Chem. Soc., 46*, 581 (1924).
10. BROTMAN, M., CULLEN, S. C., and WILKINS, D. S., " Intravenous Supplementation during Nitrous Oxide Anesthesia. Comparison of Demerol, Morphine and a New Potent Analgesic Drug ", *Anesthesiology, 11*, 527 (1950).
11. BROWN, A. K., " Methorphinan as a Supplement to Nitrous Oxide and Oxygen Anæsthesia ", *Brit. Med. Jour.*, 1331 (1952).
12. BRUSTIER, V., " Contributions à l'Etude spectrographique de l'absorption des rayons ultraviolets par les alcaloïdes et les glucosides ", *Bull. Soc. Chim., 39*, 1527 (1926).
" Ultraviolet Absorption Spectra of Alkaloids ", *Chim. et Ind., 27*, 1007 (1932).
13. CLARK, W. A., and MCBAY, A. J., " Spectrophotometric Determination of Morphine and of Codeine ", *Jour. Am. Pharm. Assoc.*, Sci. Ed., *43*, 39 (1954).
14. CRONYN, M. W., " Azabicycloalkanes. 2-Azabicyclo-(3, 3, 1)-nonane " *Journ. Org. Chem., 14*, 1013 (1949).
15. CURRERI, A. R., GALE, J. W., and DICKIE, H. A., " Effectiveness of Dromoran (3-Hydroxy-N-methylmorphinan) as an Analgesic in Thoracic Surgery ", *Jour. Thoracic Surg., 20*, 90 (1950).
16. DEDE, L., and ROSENBERG, A., " Über innere Molekülverbindungen ", *Ber., 67B*, 147 (1934).
17. DOBBIE, J. J., LAUDER, A., and TINKLER, C. K., " The Constitution of Cotarnine ", *Jour. Chem. Soc., 83*, 598 (1903).
" The Relative Strengths of the Alkaline Hydroxides and of Ammonia as measured by their Action on Cotarnine ", *Jour. Chem. Soc.*, 85, 121 (1904).
18. DOBBIE, J. J., and LAUDER, A., " On the Relation between the Absorption Spectra and the Chemical Structure of Corydaline, Berberine and other Alkaloids ", *Jour. Chem. Soc.*, 83, 605 (1903).
" The Absorption Spectra of Laudanine and Laudanosine in Relation to Their Constitution ", *Jour. Chem. Soc., 83*, 626 (1903).
" The Absorption Spectra of Cinchonine, Quinine, and Their Isomerides ", *Jour. Chem. Soc., 99*, 1253 (1911).
" The Absorption Spectra of Neopine ", *Jour. Chem. Soc., 99*, 34 (1911).
19. DOBBIE, J. J., and FOX, J. J., " Relation between the Absorption Spectra and the Constitution of Certain Isoquinoline Alkaloids and the Alkaloids of Ipecacuanha ", *Jour. Chem. Soc., 105*, 1639 (1914).
20. Document E/1998 issued by the Economic and Social Council, Department of Social Affairs, United Nations.
21. Drug Submission by Hoffmann-LaRoche, Inc., Nutley, N.J., to the Department of National Health and Welfare, Ottawa, Canada, April 3, 1951.
22. EDWARDS, L. J., " The Hydrolysis of Aspirin. A Determination of the Thermodynamic Dissociation Constant and a Study of the Reaction Kinetics by Ultraviolet Spectrophotometry ", *Trans Farad. Soc., 46*, 723 (1950).
23. ELVIDGE, W. F., " Absorption Spectrophotometry in Pharmaceutical Analysis ", *Quart, Journ. Pharm. Pharmac., 13*, 219 (1940).
23a. FARMILO, C. G., " The Ultraviolet Spectrophotometric Method ", *Bulletin on Narcotics, 6*, 3-4 (1954).
24. FISCHER, H., " Die Anwendung der Gerichtlichen Medizin als Feststellungsmethodik speziell zum Toxikologischen Nachweis von Alkaloiden ". Inaugural Dissertation zur Erlangung der Doktorwürde der Medizinischen Fakultät der Universität Zürich. Buchdruckerei Stäfa, A. G. vorm. E. Gull, Zürich, 1925.
" Die Physikalische Chemie in der Gerichtlichen Medizin und in der Toxikologie mit spezieller Berücksichtigung der Spektrographie und der Fluoreszenz Methoden ". Kommissionsverslag der Buchhandlung A. Rudolf, Zürich 1925.
25. FLEXSER, L. A., HAMMETT, L. P., and DINGWALL, A., "The Determination of Ionization by Ultraviolet Spectrophotometry. Its Validity and its Application to the Measurement of the Strength of Very Weak Bases ", *Jour. Am. Chem. Soc., 57*, 2103 (1935).
26. FOSTER, C. E., and MACDONALD, J., " The Ultraviolet Spectrum of Papaverine Hydrochloride ", *Jour. Pharm. Pharmac., 3*, 127 (1951).
27. FOX, J. J., and SHUGAR, D., " Absorption Spectra and Structure of Barbituric Acid Derivatives as a Function of pH ", *Bull. Soc. Chim. Belg., 61*, 44 (1952).
28. FRASER, H. F., and ISBELL, H., " Addiction Liabilities of Morphinan, 6-Methyldihydromorphine and Dihydrocodeinone ", *Jour. Pharmac. Exptl. Therap., 100*, 128 (1950).
29. FROMHERZ, K., *Arch. Int. Phamacodyn., 85*, 387 (1951).
30. FULTON, C. C., " Alkaloids and Their Reagents ", *Amer. Jour. Phar., 3*, 183 (1939).
31. GINSBURG, D., " The Synthesis of Morphan. 2-Azabicyclo-(3, 3, 1)-nonane ", *Jour. Org. Chem., 15*, 1003 (1950).
32. GLAZEBROOK, A. J., " Actions and Uses of Methorphinan ", *Brit. Med. Jour.*, 1328 (1952).
33. GOLDBAUM, D. S., " A Spectrophotometric Determination of Isonicotinic Acid Hydrazide ", *Science, 120*, (No. 3112), 315 (1954).
34. GOLDBAUM, L. R., " Determination of Barbiturates. Ultraviolet Spectrophotometric Method with Differentiation of several Barbiturates ", *Anal. Chem., 24*, 1604 (1952).
35. GOLDBAUM, L. R., Private Communication. " The Application of Paper Chromatography in the Analysis of Alkaloids ", by Leo R. GOLDBAUM and Leo KAZYAK.
36. GOLDBAUM, L. R., and KAZYAK, L., " The Determination of Morphine in Urine using Paper Ionophoresis and Ultraviolet Spectrophotometric Analysis ", *Jour. Pharmac., Exptl. Therap., 106*, (4), (1952).
37. GRADWOHL, R. B. H., " Legal Medicine ", The C. V. Mosby Co., St. Louis, Mo. (1954). Chapter 24, " Toxicology " by Sidney Kaye and Leo R. Goldbaum, pp. 599-723.
38. GREWE, R., " Das Problem der Morphin-Synthese " *Die Naturwissenschaften, 33*, 333 (1946) (Translation to be found in United Nations Economic and Social Council publication, E/CN 7/154, 17 Feb. 1949).
39. GREWE, R., " Synthesen in der Phenanthrene-Reihe ", *Berichte, 72*, 426, 785, 1314 (1939); *76*, 1072, 1076 (1943).
39a. GREWE, R., " Synthetische Arzneimittel mit Morphin-Wirkung ", *Angewandte Chemie, 59*, 194 (1947).
40. GREWE, R., and Mondon, A., " Synthese des Morphinans ", *Berichte, 81*, 279 (1948).
41. GRUBER, Jr., C. M., Soo LEE, K., and GRUBER, C. M., " A Comparison of the Actions of Meperidine, NU-1196, Methadone, Morphine, NU-2206 and Metapon upon the Intestine and Uterus ", *Jour. Pharmac. Exptl. Therap., 99*, 317 (1950).
41a. GULLAND, J. M. and ROBINSON, R., " Constitution of Codeine and Thebaine ", *Mem. Proc. Manchester Lit. Phil. Soc., 69*, 79 (1955).
42. HAGEMEYER, G., *Mediz. Welt, 20*, 1286 (1951).
43. HARNASCH, H., *Münch. Mediz. Wschr.* (4), 164 (1952).
44. HARTLEY, W. N., " The Absorption Spectra of Alkaloids ", Phil. Trans. Roy. Soc., London, *176*, 471, 516 (1885).
45. ISBELL, H., and FRASER, H. F., " Human Pharmacology and Addiction Liability of Derivatives of 3-Hydroxy-N-methylmorphinan ", *Jour. Pharmac. Exptl. Therap., 103*, 348 (1951).
" Actions and Addiction Liabilities of Dromoran Derivatives in Man ", *Jour. Pharmac. Exptl. Therap., 107*, 524 (1953).

46. JACKSON, G. R., WESCHLER, J. R., and DANNLEY, R. L., " Ultraviolet Absorption Spectra of the Hydrolysis Products of Diethyl barbituric Acid ", *Anal. Chem., 26*, 1661 (1954).

47. JAGGARD, R. S., ZAGER, L. L., and WILKINS, D. S., " Clinical Evaluation of Analgesic Drugs. A Comparison of NU-2206 and Morphine Sulfate administered to Postoperative Patients ", *Arch. Surg., 61*, 1073 (1950).

48. JUNKERMAN, C. L., HEEN, R. C., and POHLE, H. W., " Clinical Experience with a New Analgesic Agent ", *Jour. Lab. Clin. Med., 34*, 1615 (1949).

49. KATO, S., and SOMENO, F., " Absorption Spectrum and Molecular Structure ", Sci. Papers Inst. Phys. Chem. Research (Tokyo), *33*, 209 (1937), *34*, 905 (1938).

50. KEUTMANN, E., and FOLDES, F. F., " The Analgesic Effect of Dromoran Hydrobromide in Postoperative Pain ", *New England Jour. Med., 244*, 286 (1951).

51. KITASATO, Z., " Beiträge zur Kenntnis der Isochinolin Alkaloide ", *Acta Phytochimica*, Vol. 2 (No. 2), 175 (1927).

52. KUMLER, W. D., and STRAIT, L. A., " The Ultraviolet Absorption Spectra and Resonance in Benzene Derivatives ", *Jour. Amer. Chem. Soc., 65*, 2349 (1943).

52a. LEVI, L., HUBLEY, C. and HINGE, R., " Infrared Spectra of Narcotics and Related Alkaloids ", *Bull. Narcotics, 7*, 1 (1955).

53. LEVI, L., and FARMILO, C. G., " Reaction of Morphine with Potassium Mercuric Iodide ", *Anal. Chem., 26*, 1040 (1954).

54. LEVI, L., and FARMILO, C. G., " The Characterization of Narcotics as Reineckates ", *Can. Jour. Chem., 30*, 783 (1952).

55. LOOFBOUROW, J. R., and STIMSON, M. M., " Ultraviolet Absorption Spectra of Nitrogenous Heterocyclic Compounds ", *Jour. Chem. Soc.*, 1275 (1940).

56. LOTHIAN, G. F., " Absorption Spectrophotometry ", Hilger and Watts, Ltd., London, 1949.

57. MORGAN, Ch. E., and CEPRINI, M. Q., " Buffered Drug Solutions for Measurement of Ultraviolet Absorption at various pH's ". Reprints of this paper may be obtained from Ch. E. Morgan, Chief Chemist, State of New York, Department of State, Racing Commission Laboratory, 148-11 Hillside Ave., Jamaica 35, N.Y., U.S.A.

58. MORTON, R. A., and TIPPING, A. H., " A Spectroscopic Method for the Determination of Dissociation Constants ", *Jour. Chem. Soc.*, 1398 (1926).

59. MÜHLAU, M., *Ärztl. Wschr., 7*, 257 (1952).

60. OSOL, A., " The Spectrophotometric Determination of the Dissociation Constants of Theophylline, Theobromine and Caffeine ", *Jour. Am. Pharm. Assoc.*, Sci. Ed., *38*, 158 (1949).

61. OESTREICHER, P. M., FARMILO, C. G., and LEVI, L., " Ultraviolet Spectral Data for Ninety Narcotics and Related Compounds ", *Bull. Narcotics, 6*, 3-4 (1954).

62. PRINGSHEIM, P., " Fluoreszenz und Phosporeszenz im Lichte der Neuen Atom Theorien ", J. Springer Verlag, Berlin, 1921.

63. RANDALL, L. O., and LEHMANN, G., "Analgesic Action of 3-Hydroxy-N-methylmorphinan Hydrobromide (Dromoran) ", *Jour. Pharmac. Exptl. Therap., 99*, 163 (1950).

64. RECHENBERG, H. K., and ZEERLEDER, R., *Schweiz. Med. Wschr., 81*, 44, 1086 (1951).

65. SCHNIDER, O., and GRÜSSNER, A., " Synthese von Oxy-morphinanen ", *Helv. Chim. Acta, 32*, 821 (1949).

66. SCHNIDER, O., and GRÜSSNER, A., " Oxy-morphinane. (3. Mitteilung). Optisch aktive 3-Oxy-morphinane ", *Helv. Chim. Acta, 34*, 2211 (1951).

66a. SCHNIDER, O., and HELLERBACH, J., " Synthese von Morphinanen " (2. Mitteilung), *Helv. Chim. Acta, 33*, 1437 (1950).
" Oxymorphinane (4. Mitteilung); Synthese von Benzyl-octahydro-isochinolinen ", *Helv. Chim. Acta, 34*, 2218 (1951).

66b. Paper presented by Dr. E. L. SEVRINGHAUS, Vice-President for Chemical Research, Hoffmann-LaRoche, Inc., Nutley, N.J., before Officers of the Food and Drug Directorate and the Division of Narcotic Control, Ottawa, Feb. 14, 1951.

67. SIEGEL, B. M., BLOCH, D. P., PITESKY, I., and LAST, J. H., " Comparative Study of Morphine and Dromoran as Antidiuretic Agents in the Dog ", *Proc. Soc. Exptl. Biol. Med., 74*, 809 (1950).

68. SLOMKA, M. B., and GROSS, E. G., " An Evaluation of the Analgesic Activity of the Dromoran Isomers ", *Proc. Soc. Exptl. Biol. Med., 81*, 548 (1952).

69. SMITH, H. W., and MACDOUGAL, J. R., " A Compilation of Spectrophotometric Data on Compounds of Toxicological Interest ". Attorney General's Laboratory, Toronto, Canada, May 1953.

70. SMITH, R. M., " Clinical Experience with Dromoran Hydrobromide (NU-2206) for the Relief of Chronic Pain ", *South. Med. Surg., 112*, 251 (1950).

71. STENSTRÖM, W., and GOLDSMITH, N., " Determination of Dissociation Constants of Phenol and the Hydroxyl Group of Tyrosine by means of Absorption Measurements in the Ultra-Violet ", *Jour. Phys. Chem., 30*, 1683 (1926).

72. STENSTRÖM, W., and REINHARD, M., " The Influence of the pH upon the Ultraviolet Absorption Spectra of Certain Cyclic Compounds ", *Jour. Phys. Chem., 29*, 1477 (1925).

73. STIMSON, M. M., and REUTER, M. A., " Spectrophotometric Estimation of Methoxycinchona Alkaloids ", *Jour. Am. Chem. Soc., 68*, 1192 (1946).

74. STOELTING, V. K., THEYE, R. A., and GRAF, J. P., *Anesthesiology, 12*, 225 (1951).

75. STUCKEY, R. E., " The Ultraviolet Absorption Spectra of Barbituric Acid and its 1-Methyl and 1, 3-Dimethyl Derivatives ", *Quart. Jour. Pharm. Pharmac., 13*, 312 (1940).
" The Absorption Spectra of Organic Compounds containing Nitrogen. Part. I. Derivatives of Hydantoin ", *Jour. Chem. Soc.*, 331 (1947).
" The Applications of Ultraviolet Absorption Spectrophotometry in Pharmaceutical Analysis ", *Jour. Pharm. Pharmac., 4*, 345 (1952).

76. TREADWELL, F. P., and HALL, W. T., " Analytical Chemistry ". John Wiley & Sons, Inc., New York, 1952. Vol. I, pp. 281, 321, 522.

77. VANDENBELT, J. M., and DOUB, L., " The Ultraviolet Absorption Spectra of Simple, Unsaturated Compounds ", *Jour. Am. Chem. Soc., 69*, 2714 (1947).

78. World Health Organization, Expert Committee on Drugs liable to produce Addiction, *Technical Report Series*, No. 21, March 1950, pp. 6 and 11. Note submitted by Dr. N. B. EDDY, Medical Officer, National Institutes of Health (U.S. Public Health Service), Bethesda, Md., U.S.A., based upon the work of Dr. H. ISBELL, Research Director, U.S. Public Health Services Hospital, Lexington, Ky., U.S.A.

79. World Health Organization, Expert Committee on Drugs liable to produce Addiction, *Technical Report Series*, No. 57, January 1952, pp. 6 and 7.

80. World Health Organization, Expert Committee on Drugs liable to produce Addiction, *Technical Report Series*, No. 76, March 1954, pp. 8 and 9.

81. WILKINS, D. S., CULLEN, S. C., and BROTMAN, M., *Anesthesiology, 12*, 145 (1951).

82. WOHL, A., " Étude spectrale sur les arylamines et leurs chlorhydrates ", *Bull. Soc. Chim. France, 6*, 1312 (1939).
" L'absorption dans l'ultraviolet des sels de Diazonium ", *Bull. Soc. Chim. France, 6*, 1319 (1939).

83. ZAGER, L. L., SAWTELLE, W. W., GROSS, E. G., NAGYFY, S. F., and TIDRICK, R. T., " Observations on the Use of a New Analgesic, NU-2206 (3-Hydroxy-N-methylmorphinan Hydrobromide) ", *Jour. Lab. Clin. Med., 34*, 1530 (1949).

Microchemical Identification of Dromoran

BREINLICH, J., " Der Mikrochemische Nachweis einiger Analgetika, insbesondere Polamidon und Ticarda " Höchst ", Cliradon " Ciba " und Dromoran " Roche ", *Arzneimittel Forschung, 3*, 93 (1953).
" Nachweis von Dromoran und Cliradon neben Morphin im Urin durch Trübungsmethoden ", *Arzneimittel Forschung, 3*, 212 (1953).
" Zum Mikrochemischen Nachweis von Cliradon und Dromoran ", *Arzneimittel Forschung, 3*, 490 (1953).

BROSSI, A., HAEFLIGER, O., SCHNIDER, O.: " Oxy-morphinane. 6. Die papierchromatographische Bestimmung von Morphinanderivaten und die Verfolgung ihrer Ausscheidung beim Hund ", *Arzneimittel-Forschung*, Feb. 1955, *5* : 2, pp. 62-66.

GOLDBAUM, L. R., " The Application of Paper Chromatography in the Analysis of Alkaloids ". Private communication.

JATZKEWITZ, H., " Ein Klinisches Verfahren zur Bestimmung von Basischen Suchtmitteln in Harn ", *Hoppe-Seyler's Zeitschr. Physiol. Chem.*, *292*, 94 (1953).

KAISER, H., and JORI, H., " Beiträge zum Toxikologischen Nachweis von Dromoran ' Roche ', Morphin, Dilaudid, Cardiazol, Coramin und Atropin mit Hilfe der Papierchromatographie ", *Pharmaz. Ztg.-Nachr.*, *88*, 963 (1952); *Archiv der Pharmazie*, *287*, 224 (1954).

VIDIC, E., " Nachweis, Unterscheidung und Quantitative Bestimmung stark wirkender synthetischer Analgetika, insbesondere des Cliradon, im Urin ", *Arzneimittel Forschung*, *3*, 34 (1953).

" Nachweis und Quantitative Bestimmung des Dromoran ", *Arzneimittel Forschung*, *3*, 428 (1953).

" Zum Mikrochemischen Nachweis von Cliradon und Dromoran ", *Arzneimittel Forschung*, *3*, 490 (1953).

OFFICIAL

United Nations Documents Dealing with Narcotic Drugs

Volume V, No. 1, of the *Bulletin* contained a list of the more important United Nations documents relating to narcotic drugs issued up to 31 December 1952. The documents now listed, issued between January 1953 and March 1955, contain a variety of information —legal, technical, administrative, etc. The list is not comprehensive, documents of ephemeral interest having been omitted. Documents have in most cases been listed under only one main heading, though it will be appreciated that to a considerable extent the topics are interlocking.

These documents can be consulted either at the permanent Headquarters of the United Nations in New York or at the United Nations Library in Geneva.

The documents are listed under the following heads:

I. General accounts of the work of the international bodies on narcotics drugs.
II. Control.
III. Illicit traffic.
IV. Single Convention.
V. 1953 Opium Protocol.
VI. Opium and Opiates.
VII. Coca leaf and derivatives.
VIII. Cannabis and derivatives.
IX. Synthetic narcotic drugs.
X. Drug addiction.

I. General Accounts of the Work of the International Bodies on Narcotic Drugs

1. *Commission on Narcotic Drugs*

E/CN.7/249	Progress Report of the Division of Narcotic Drugs for the period 21 March to 31 December 1952.	18 February 1953
/Add.1	Ditto, covering the period 1 January to 28 February 1953.	20 March 1953
E/CN.7/264	Progress Report of the Division of Narcotic Drugs for the period 1 March to 31 December 1953.	2 March 1954
/Add.1	Ditto, covering the period 1 January to 15 March 1954.	19 March 1954
E/CN.7/289 and Corr.1	Report of the Division of Narcotic Drugs for the period 15 March to 31 December 1954.	21 February 1955
/Add.1	Ditto, covering the period 1 January to 15 March 1955.	4 April 1955
E/2423-E/CN.7/262	Report of the eighth session of the Commission on Narcotic Drugs.	7 May 1953
E/2606-E/CN.7/283	Report of the ninth session of the Commission on Narcotic Drugs.	4 June 1954
E/2768-E/CN.7/303 and Corr.1	Report of the tenth session of the Commission on Narcotic Drugs.	8 June 1955
E/CN.7/SR.189-223	Summary Records of the 189th-223rd meetings (eighth session of the Commission).	30 March-24 April 1953
E/CN.7/SR.224-260	Summary Records of the 224th-260th meetings (ninth session of the Commission).	19 April-14 May 1954
E/CN.7/SR.261-294	Summary Records of the 261st-294th meetings (tenth session of the Commission).	18 April-12 May 1955

2. *Permanent Central Opium Board*

E/OB/9	Report to the Economic and Social Council on statistics of narcotics for 1952 and the work of the Board in 1953.	November 1953
/Add.1	Ditto.	December 1953
E/OB/10	Report to the Economic and Social Council on statistics of narcotics for 1953 and the work of the Board in 1954.	November 1954
/Add.1	Ditto.	December 1954
E/OB/11	Report to the Economic and Social Council on statistics of narcotics for 1954 and the work of the Board in 1955.	November 1955

3. *Drug Supervisory Body*

E/DSB/11	Estimated World Requirements of Narcotic Drugs in 1954.	15 December 1953
/Add.1	Ditto.	31 March 1954
/Add.2	Ditto.	30 June 1954
/Add.3	Ditto.	30 September 1954
/Add.4	Ditto.	31 December 1954
E/DSB/12	Estimated World Requirements of Narcotic Drugs in 1955.	15 December 1954
/Add.1	Ditto.	31 March 1955
/Add.2	Ditto.	30 June 1955
Ditto.	Ditto.	30 September 1955
E/DSB/13 and Add.	Estimated World Requirements of Narcotic Drugs in 1956.	15 December 1955

4. *Economic and Social Council*

A/2430	Report of the Economic and Social Council covering the period from 2 August 1952 to 5 August 1953 : Chapter IV, Section IV.	1953
E/2419	Resolutions of the Economic and Social Council, fifteenth session : No. 477 (XV).	12 May 1953
E/2508	Ditto, sixteenth session : No. 505 (XVI).	15 August 1953
A/2686	Report of the Economic and Social Council covering the period from 6 August 1953 to 6 August 1954 : Chapter IV, Section IV.	1954
E/2654	Resolution of the Economic and Social Council, eighteenth session : No. 548 (XVIII).	15 August 1954
A/2943	Report of the Economic and Social Council covering the period from 7 August 1954 to 5 August 1955 : Chapter V, Section V.	1955
E/2795	Resolutions of the Economic and Social Council, twentieth session : No. 588 (XX).	15 August 1955

5. *General Assembly*

A/2361	Resolutions of the General Assembly, seventh session : No. 674 (VII).	February 1953
A/2630	Resolutions of the General Assembly, eighth session : No. 774 (VIII), No. 786 (VIII).	January 1954
A/2890	Ditto, ninth session : No. 834 (IX), No. 886 (IX), No. 890 (IX).	February 1955
A/2731	Organization of the Secretariat (Report of the Secretary-General).	21 September 1954

6. *World Health Organization*

	Reports of the Expert Committee on Drugs Liable to Produce Addiction	
First Report	Official Records of the World Health Organization.	1949, ***19***
Second Report	World Health Organization. Techn. Rep. Ser.	1950, ***21***
Third Report	" " " "	1952, ***57***
Fourth Report	" " " "	1954, ***76***
Fifth Report	" " " "	1955, ***95***

II. Control *

E/NR.19../..	Under Article 21 of the 1931 Convention, governments are bound to furnish annual reports covering their work in the field of narcotics. The Secretariat receives approximately 120 such reports every year.**	
E/NR.1953/FORM	Form of Annual Reports to be communicated by governments to the Secretary-General, in accordance with Article 21 of the 1931 Convention.	28 July 1953
E/NR.1954/FORM	Ditto.	1 June 1954
E/NR.1955/FORM	Ditto.	1 June 1955
E/CN.7/251	Draft amendments to the form of Annual Reports (Note by the Secretary-General).	29 January 1953
/Add.1	United Kingdom : Comments.	25 March 1953
E/CN.7/271	Revision of the form of Annual Reports (Note by the Secretary-General).	9 April 1954
E/CN.7/290	Comments by governments on the draft revised form of Annual Reports.	10 March 1955
/Add.1	Ditto. Netherlands : Comments.	19 April 1955
/Add.2	Ditto. Switzerland : Comments.	3 April 1955
E/NR.19../Summary	A summary of the Annual Reports covering each calendar year is published by the Secretariat.	
E/NL.19../..	Under Article 21 of the 1931 Convention, governments are bound to furnish the laws and regulations dealing with narcotics promulgated during each year. The Secretariat receives approximately 100 such laws every year.	
E/NL.19../Summary	A summary of these laws is issued yearly by the Secretariat.	
E/NA.1953/1 and Corr.1	List of national authorities empowered to issue certificates and authorization for the import and export of narcotic drugs (issued by the Secretariat).	10 February 1953
E/NA.1955/1	Ditto.	23 June 1955
E/NF.1953/1 and Corr.1 and 2	List of firms authorized to manufacture drugs (issued by the Secretariat).	23 January 1953
E/CN.7/247 and Corr.1	List of the basic narcotic drugs coming under the international narcotics treaties (issued by the Secretariat).	23 January 1953
E/CN.7/244	Abolition of opium-smoking : reports transmitted by governments in accordance with resolution 159 II B (VII) of the Economic and Social Council.	17 November 1952
/Add.1	Ditto. Pakistan.	28 January 1953
/Add.2	Ditto. Laos.	12 March 1953
/Add.3	Ditto. Cambodia.	19 March 1953
E/CONF.14/4 and Corr.1	The abolition of opium-smoking (Note by the Secretary-General giving the background information and showing the post-war situation).	12 March 1953
E/CN.7/265	Abolition of opium-smoking : reports transmitted by governments in accordance with resolution 159 II B (VII) of the Economic and Social Council.	9 February 1954
/Add.1	Ditto. Burma.	20 April 1954
E/CN.7/281	Report on the abolition of opium-smoking in Cambodia for the year 1953.	20 April 1954
E/CN.7/284	Abolition of opium-smoking : reports transmitted by governments in accordance with resolution 159 II B (VII) of the Economic and Social Council.	24 May 1954
E/CN.7/245	Memorandum by the Secretary-General on the co-operation between the United Nations and the Universal Postal Union in the international control of narcotic drugs.	19 January 1953
E/CN.7/253	Regulations on the trade in narcotics in the Benelux area (Note by the Secretary-General).	24 March 1953
E/CONF.14/11	The status of multilateral conventions (Note by the Secretary-General).	29 April 1953
E/CN.7/291	Question of official forms for the prescription of narcotics (Note prepared by the Secretariat in consultation with the World Health Organization).	7 April 1955

* For the work of the Permanent Central Opium Board and the Supervisory Body, see Section I, 2 and 3, above.

** From 1954 the annual reports are not published in separate fascicules.

III. Illicit Traffic *

E/NS.1952/Summary 1.	Six summaries of illicit transactions and seizures published yearly, in 1952 and 1953, ten in 1954, and twelve to be published in 1955.	
E/CN.7/246	Replies of governments to the Burmese proposal for co-ordinating the efforts of certain Far Eastern governments to suppress poppy cultivation and the smuggling of opium (E/CN.7/222).	20 January 1953
E CONF.14/9 and Corr.1	Illicit traffic in opium (Note by the Secretary-General).	19 March 1953
E/CN.7/252	Memorandum by the Secretary-General on the illicit traffic in narcotic drugs during 1952.	24 March 1953
E/CN.7/254	Memorandum by the International Criminal Police Commission on illicit traffic in narcotic drugs in 1952.	6 May 1953
E/CN.7/257	Communications of governments on the control of illicit traffic in narcotic drugs.	30 January 1953
E/CN.7/267	Illicit traffic : communication from the Administrator of the Zone of Tangier.	5 March 1954
E/CN.7/272	Memorandum by the Secretary-General on the illicit traffic in narcotic drugs during 1953.	12 April 1954
E/CN.7/273	Memorandum by the International Criminal Police Commission on illicit traffic in narcotic drugs in 1953.	12 March 1954
E/CN.7/274	Illicit traffic. International co-operation : Economic and Social Council resolution 435 C (XIV).	5 March 1954
/Add.1	Ditto. Communication from France.	27 April 1954
E/CN.7/292	Review of the illicit traffic in narcotic drugs during 1954 (Note by the Secretary-General).	18 April 1955
E/CN.7/293	Memorandum by the International Criminal Police Commission on illicit traffic in narcotic drugs in 1954.	17 March 1955
E/CN.7/294	Procedures of the Commission for reviewing the situation in the illicit traffic (Note by the Secretary-General).	15 March 1955

IV. Single Convention **

E/CN.7/AC.3/4/Rev.1	Commentary on the draft Single Convention (Note by the Secretary-General).	4 June 1952
E/CN.7/AC.3/5/Add.1	Observations of the Government of India on the draft Single Convention.	17 June 1952
E/CN.7/AC.3/6	Partial redraft of the Single Convention (Note by the Secretary-General).	9 December 1952
/Add.1	Ditto.	26 April 1954
E/CN.7/L.48	The proposed Single Convention (Note by the Secretary-General : observations of the Permanent Central Opium Board).	2 March 1954
E/CN.7/L.85 and Corr.1	Draft provisions concerning the problem of synthetic drugs, for incorporation in the Single Convention (Working paper by the Secretary-General).	12 January 1955
E/CN.7/L.86	Working paper by the Secretary-General on the proposed Single Convention.	7 February 1955
/Add.1	Ditto. Observations on the time-limit for sending in quarterly statistics of imports and exports of narcotic drugs.	24 March 1955
E/CN.7/L.89	Proposed article relating to the control of the manufacture of narcotics (E/CN.7/AC.3/3, section 34, as revised. Communication from the Austrian Government.	11 March 1955
E/CN.7/295	Memorandum on the utilization and control of poppy straw (Note by the Secretary-General).	11 February 1955
E/CN.7/289 and Corr.1	Report of the Division of Narcotic Drugs for the period 15 March to 31 December 1954, Chapter VI, paragraphs 108-110.	21 February 1955

* See also Chapter V on Illicit Traffic in Annual Reports of Governments, E/NR.19.../....

** *See also:*

E 2423-E/CN.7/262	Report of the Commission (eighth session), Chapter III (pp. 8-14) and Annex C.	7 May 1953
E 2606-E/CN.7/283	Report of the Commission (ninth session), Chapter III (pp. 8-11) and Annexes D and E.	4 June 1954
E 2768-E/CN.7/303 and Corr.1	Report of the Commission (tenth session), Chapter III (pp. 31-61) [mimeographed form] and Annex D.	8 June 1955

V. 1953 Opium Protocol *

E/CONF.14/10 and Corr.1	Historical survey of attempts to achieve the international limitation of opium production (Note by the Secretary-General).	17 April 1953
E/2186	Compendium of observations of Governments on the proposed Opium Protocol.	14 March 1952
/Add.1	Ditto. Austria, Ireland.	9 April 1952
/Add.2	Ditto. India, Indonesia.	19 May 1952
/Add.3	Ditto. Cuba.	21 May 1952
E/CONF.14/1	Compilation of observations of governments on the draft Protocol.	4 February 1953
/Add.1	Ditto. Ireland.	8 April 1953
Add.2 and Corr.1	Ditto. India.	1 May 1953
E/CONF.14/2	Observations of the Permanent Central Opium Board and the Drug Supervisory Body on the draft Protocol.	6 February 1953
E/CONF.14/15	International enforcement measures of the draft Protocol on Opium (Note by the Secretary-General).	25 May 1953
/Add.1	Ditto.	22 May 1953
E/NT/8	Protocol for Limiting and Regulating the Cultivation of the Poppy Plant, the Production of, International and Wholesale Trade in, and Use of Opium.	28 September 1953
E/CN.7/275	Provisional draft of a model code and commentary for the application of the Protocol (Note by the Secretary-General).	14 April 1954
/Add.1	Ditto.	13 April 1954
E/CN.7/285 and Corr.2	Draft of a model code for the application of the Protocol [Draft text of the Rapporteur].	17 February 1955
E/CN.7/287	Observations of Governments represented on the Commission concerning the draft of a model code and commentary for the application of the Protocol (E/CN.7/275/Add.1).	20 January 1955
/Add.1	Ditto. Turkey.	27 April 1955
E/NT/9	Model guide for the application of the Protocol.	October 1955

VI. Opium and Opiates **

E/CONF.14/12	General note on the opium poppy (Note by the Secretary-General).	4 March 1953
E/CONF.14/3	Quasi-medical use of opium (Note by the Secretary-General).	10 March 1953
E/CONF.14/5	The occurrence of the opium alkaloids in opium and the poppy plant (Note by the Secretary-General).	13 March 1953
E/CONF.14/6	Artificial opium alkaloids (Note by the Secretary-General).	13 March 1953
E/CONF.14/7 and Corr.1	The manufacture of morphine from poppy straw (Note by the Secretary-General).	13 March 1953
/Add.1	Ditto. Recent statistics.	12 May 1953
E/CONF.14/8	Legal provisions concerning national opium agencies in opium-producing countries (Note by the Secretary-General).	18 May 1953
E/CONF.14/9 and Corr.1	Illicit traffic in opium (Note by the Secretary-General).	19 March 1953
E/CONF.14/14 and Corr.1	Statistics on opium, the manufacture of morphine and of synthetic narcotic drugs, for the years 1946 to 1951 (Note by the Secretary-General).	6 May 1953
/Add.1 and Add.1/Corr.1	Ditto. Year 1952.	13 May 1953
ST/SOA/SER.K/...	The assay, characteristics, composition and origin of opium :	
ST/SOA/SER.K/13	Exhaustive extraction of the opium with lime-water in the assay procedure (United Nations Secretariat).	12 January 1953
ST/SOA/SER.K/14	The colorimetric determination of " porphyroxine meconidine " : the relation between tintometer and spectrophotometric measurements obtained in the determination of " porphyroxine meconidine " in opiums, by Dr. C. G. Farmilo and P. M. L. Kennett (Canada).	26 January 1953

* See also Section VI below.

** See also Section V.

ST/SOA/SER.K/15	An assay procedure for opium based on that of the Japanese pharmacopœia, and morphine percentages obtained on samples from various countries, by H. Asahina (Japan).	11 March 1953
ST/SOA/SER.K/16	A study of the United Nations samples of opium, by Dr. G. Panopoulos and A. Vassiliou (Greece).	24 March 1953
ST/SOA/SER.K/17	Extractive determination of thebaine and papaverine in opium (United Nations Secretariat).	25 March 1953
ST/SOA/SER.K/18	The assay for morphine in opium and determination of the total of minor phenolic alkaloids, by Dr. C. K. Liang (China).	30 April 1953
ST/SOA/SER.K/19	The colorimetric determination of " porphyroxine meconidine ". Second communication : experiments on the determination of " porphyroxine meconidine " in small quantities of opium, by L. Fuchs and W. Ullrich (Austria).	1 September 1953
ST/SOA/SER.K/20	Estimation of codeine in opium, by C. Parthasarathy and N. Rajagopalan (India).	20 July 1953
ST/SOA/SER.K/21	Classification of opium samples by microscopic test (United Nations Secretariat).	24 September 1953
ST/SOA/SER.K/22	A study of Dr. Liang's assay (ST/SOA/SER.K/18 and its extension to determination of the principal nonphenolic alkaloids of opium (United Nations Secretariat).	29 December 1953
ST/SOA/SER.K/23	Preliminary analyses of ash from different kinds of opium by Professor A. Jermstad, and T. Waaler (Norway).	21 April 1954
ST/SOA/SER.K/24	Preliminary report on the quantitative determination of some opium alkaloids by means of infra-red spectrophotometry, by Professor A. Jermstad and J. Lothe (Norway).	5 May 1954
ST/SOA/SER.K/25	A preliminary investigation of methods for determining the origin of opium, by T. S. T. Chari, C. Parthasarthy, N. Rajagopalan and K. S. Subramanian (India).	10 March 1954
ST/SOA/SER.K/26	A systematic determination of the principal alkaloids in raw opium, by Dr. C. K. Liang (China).	29 April 1954
ST/SOA/SER.K/27	A study of paper chromatography, by Dr. G. Panopoulos and A. Vassiliou (Greece).	29 April 1954
ST/SOA/SER.K/28	Trials of unknown opiums by Canadian scientists for origin determinations (United Nations Secretariat).	29 April 1954
ST/SOA/SER.K/29	Observations on the determination of the morphine content of raw opium, by Professor F. von Bruchhausen (Germany).	26 May 1954
ST/SOA/SER.K/30	The determination of countries of origin of opium samples by means of the composition of the opium ash, by J. C. Bartlet and Dr. C. Farmilo (Canada).	12 July 1954
ST/SOA/SER.K/31	Graphical comparisons of analyses of opium samples (United Nations Secretariat).	15 October 1954
/Add.1	Ditto.	15 October 1954
ST/SOA/SER.K/32 and Corr.1	Determination of morphine and codeine in opium, by H. Asahina and Y. Shiuchi (Japan).	30 August 1954
ST/SOA/SER.K/33	Researches on extracting the alkaloids from solid opium (United Nations Secretariat).	14 September 1954
ST/SOA/SER.K/34	A unified analysis of opium for alkaloids (United Nations Secretariat).	14 September 1954
ST/SOA/SER.K/35	A rapid precipitation method for narcotine and a new short method for determining morphine in opium by extraction (United Nations Secretariat).	25 August 1955
ST/SOA/SER.K/36	Additional trials of opium " unknowns " for determination of their origins, by Dr. C. Farmilo and J. Bartlet (Canada).	20 April 1955
ST/SOA/SER.K/37	Supplementary study on the method for the determination of origin of opium based on paper chromatography, by Dr. G. Panopoulos and A. Vassiliou (Greece).	4 April 1955
ST/SOA/SER.K/38	Narcotine and morphine percentages, and ratios of codeine and narcotine to morphine, in relation to the origin of opium (United Nations Secretariat).	25 August 1955
ST/SOA/SER.K/39	Detection of morphine in poppy plants by paper chromatography, by H. Asahina and M. Ono (Japan).	30 June 1955

ST/SOA/SER.K/40 and Corr.1	Determination of morphine in opium tincture by paper chromatography, by H. Asahina and M. Ono (Japan).	25 August 1955
E/2372	Establishment of a United Nations Narcotics Laboratory (Note by the Secretary-General).	27 February 1953
E/2372/Add.1-E/CN.7/269	Ditto.	1 March 1954
E/CN.7/241	Communications received by the United Nations Secretariat on scientific research into the nature of opium (U.S.S.R., France).	17 October 1952
E/CN.7/258	Scientific research on narcotics (Note by the Secretary-General on the progress made in 1952 in the programme of scientific research on opium).	16 February 1953
E/CN.7/278 and Corr.1	Report of the Committee of chemical experts on the United Nations Programme for determining the origin of raw opium by chemical and scientific means.	22 March 1954
E/CN.7/279	Scientific research on narcotics and the United Nations Narcotics Laboratory (Note by the Secretary-General).	22 April 1954
A/C.3/573	United Nations Narcotics Laboratory (Note by the Secretary-General).	15 October 1954
A/2829	Report of the Third Committee of the General Assembly, ninth session, Chapter III.	December 1954
A/2865	Report of the Fifth Committee of the General Assembly, ninth session (United Nations Laboratory—financial implications).	13 December 1954

VII. Coca leaf and Derivatives

E/CN.7/242/Rev.2	Communication from the Ministry of Public Health and Social Welfare of Peru : export of coca leaf from Peru.	17 March 1953
/Rev.2/Add.1	Ditto. Statistical data.	25 March 1953
E/CN.7/261	Communication from the Ministry of Public Health and Social Welfare of Peru : statistical data on the export of coca leaf from Peru.	30 April 1953
E/CN.7/280	Communication from the Ministry of Public Health of Colombia on the coca leaf.	12 April 1954
E/CN.7/282	The problem of the coca leaf : legislative texts transmitted by the Government of Bolivia.	22 April 1954
E/CN.7/302	The problem of the coca leaf : communication from the Government of Argentina on the problem of the coca leaf.	6 May 1955

VIII. Cannabis and Derivatives

E/CN.7/256	The problem of Indian hemp (cannabis) (Note by the Secretary-General).	19 March 1953
E/CN.7/276	The problem of cannabis : programme of studies (Note by the Secretary-General).	22 March 1954
E/CN.7/286	Programme of studies on the cannabis plant and its products : survey of the situation in the Union of South Africa (Note by the Secretary-General).	18 January 1955
/Add.1	Ditto. Survey of the situation in Basutoland.	18 January 1955
/Add.2	Ditto. Survey of the situation in Bechuanaland.	19 January 1955
/Add.3 and Corr.1	Ditto. Survey of the situation in Swaziland.	20 January 1955
/Add.4	Ditto. Addendum to the survey of the situation in the Union of South Africa.	18 February 1955
/Add.5	Ditto. Addendum to the survey of the situation in Basutoland.	11 March 1955
/Add.6	Ditto. Survey of the situation in Northern Rhodesia.	30 March 1955
/Add.7 and Corr.1	Ditto. Survey of the situation in Southern Rhodesia.	30 March 1955
/Add.8	Ditto. Survey of the situation in Brazil.	19 April 1955
E/CN.7/297	The possibility of replacing hemp fibre and hempseed by other crops of similar industrial value or of developing narcotic-free strains of the cannabis plant (Study by Food and Agriculture Organization in consultation with United Nations Secretariat).	24 March 1955

E/CN.7/298	Replies of Governments regarding Council resolution 548 F II (XVIII) and scientific research on cannabis.	1 April 1955
/Add.1	Ditto.	19 April 1955
/Add.2	Ditto.	20 April 1955
/Add.3	Ditto.	22 April 1955
E/CN.7/304	Chemical and physical methods of analysis of resin, by Dr. C. G. Farmilo (Canada).	15 June 1955
E/CN.7/L.92	The question of cannabis : note by the representative of Greece.	20 April 1955

IX. Synthetic Narcotic Drugs

E/CN.7/255	Control of synthetic narcotic drugs : communications from governments.	30 January 1953
E/CN.7/259/Rev.1	The problem of synthetic drugs (extension of international control to synthetic drugs) (Note by the Secretary-General).	20 March 1953
E/CN.7/260	A survey of the synthetic narcotic drugs, their salts and preparations placed under national control in the various countries and territories (Note by the Secretary-General).	23 March 1953
E/CN.7/268	Chemical aspects of synthetic substances with morphine-like effect (Study by the World Health Organization, in consultation with United Nations Secretariat).	10 March 1954
E/CN.7/277	Compilation of the views of governments on the use and control of synthetic narcotic drugs transmitted in accordance with resolution 505 C (XVI) of the Economic and Social Council.	26 March 1954
/Add.1	Ditto. India.	4 May 1954
/Add.2	Ditto. Iran.	18 January 1955
E/CN.7/299	Synthetic substances with morphine-like effect : relationship between chemical structure and analgesic action (Study by World Health Organization, in consultation with United Nations Secretariat).	30 March 1955
E/CN.7/L.47	The problem of synthetic narcotic drugs (Programme of technical work) (Note by the Secretary-General).	25 February 1954

X. Drug Addiction

E/CN.7/270	Drug addiction : international aspects of the problem (Note by the Secretary-General).	5 March 1954
E/CN.7/296	Summary of state legislation in the United States relating to the treatment of drug addiction (Prepared by the Library of Congress).	1 April 1955
E/CN.7/L.87	Excerpts from the summary records of the United Nations Seminar on the Prevention of Crime and Treatment of Offenders for Asia and the Far East.	10 February 1955

Sir Atul Chatterjee

On 8 September 1955, Sir Atul Chatterjee, G.C.I.E., K.C.S.I., died at Bexhill, England.

Sir Atul Chatterjee was a well-known figure in the international control of narcotic drugs as a member of the Permanent Central Opium Board. Born in 1874, he was educated at Presidency College, Calcutta, and King's College, Cambridge. He was, from the start of his brilliant career, interested in the economic and social aspects of human activity, and during his long life was always a model of hard work and high ideals. Representative of India at the 1927 League of Nations Assembly, a Vice-President of the Consultative Economic Committee of the League, Delegate of India to the London Naval Conference of 1930 and President of the Governing Body of the International Labour Organisation, he was also High Commissioner for India in London, where his initiative and effort resulted in the building of India House in Aldwych, which stands as a monument to his memory.

Sir Atul Chatterjee left his mark in the field of thought and scholarship in *A Short History of India* written in collaboration with W. H. Moreland, and *The New India*, works which are of the greatest value in the understanding of his country. The editors of the *Bulletin* wish to extend their heartfelt condolences to his family.

Monsieur Gaston Bourgois

Gaston Louis Georges Bourgois, who died in 1955, was one of the most important figures of the International Control of Narcotic Drugs, one of those who had contributed most to its development and its success.

Born on 10 May 1874, Gaston Bourgois had a very diversified career and his activity never slowed down in the course of his long life. He was a student at the École Polytechnique and became an officer first in the Artillery, then in the Navy, and a scholar in mathematics. He was interested in linguistics and made a second career as an interpreter for Far Eastern languages : his knowledge of Japanese permitted him to become one of the best Western specialists of Japanese mathematics.

As a diplomat finally, he held various positions, especially in Siberia, where he was Vice-Consul in 1919, Estonia and Switzerland.

In the field of narcotics he contributed much to the development of international control : in 1924 he was the representative of France to the European Conferences in Geneva and signed as a plenipotentiary the Opium Convention of 19 February 1925. He was the head of the French delegation to the Conference for Limiting the Manufacture of Narcotic Drugs and one of the main authors of the Convention which was signed at Geneva on 13 July 1931 as a conclusion of that Conference. He took part in the work of the Bangkok Conference of 1931 and of the Conference for the Repression of Illicit Traffic of 1936 and after the war he became a member of the Commission of Narcotic Drugs of the United Nations. As a representative of France to that Commission he took part in the drafting of the Protocols of 1946 and 1948.

All those who had occasion to work with Gaston Bourgois remember not only his extreme intelligence and his broad knowledge of the problems of narcotics, but at the same time his profound humanity, which caused him to intervene in the debates at critical moments in order to remind his colleagues of the aim which was to be reached. In a speech he made at the second session of the Commission, he showed clearly the purposes he was aiming at :

> " We have now a new international law . . . which is a great threefold achievement : administrative, legal, social; . . . not simply the development of technique in co-operation between States but rather the evolution of that spirit itself which inspires our co-operation, which animates and leads it. A new spirit prevails, a new conception of the reciprocal rights and duties of the States has developed, a new international conscience has come to life. There is in this a great, a very great lesson, for its is a lesson of optimism and hope."

The whole life of Gaston Bourgois was itself a lesson of optimism and hope. The editors of the *Bulletin* wish to extend to his family their heartfelt condolences.

Bibliography

SCIENTIFIC PUBLICATIONS ON NARCOTIC DRUGS FOR 1954 (COMPLEMENT)

Introduction

The following bibliography is complementary to the one published in Volume VII, No. 2. It includes scientific publications on narcotic drugs which appeared during 1954 but could not, for various technical reasons, be included in the preceding bibliography. The present work has no claim to be complete and information regarding books or articles not included in it would be gratefully received by the Division of Narcotic Drugs, European Office of the United Nations, Geneva, Switzerland.

As in the preceding one, this bibliography has been arranged by subject in the following way :

Part I. General and reference works

Part. II. Opium poppy, opium and drugs manufactured therefrom

- A. Opium poppy, opium and opium alkaloids collectively considered
- B. Morphine, Apomorphine
- C. Other phenanthrene alkaloids and derivatives of opium
- D. Other drugs and substances derived from the opium poppy

Part III. The coca leaf and cocaine

Part IV. Cannabis and its derivatives

Part V. Synthetic drugs

- A. General works
- B. Pethidine and related compounds
- C. Methadone and related compounds
- D. Morphinan and morphine synthesis

Part VI. Addiction to narcotic drugs

Under each heading, publications are arranged alphabetically by author. Owing to the nature of the sources available to the secretariat for preparing this bibliography, several titles are given in translation only. They are preceded by an asterisk.

Part. I GENERAL AND REFERENCE WORKS

A

ANONYMOUS : Habit-forming and potentially harmful drugs : a guide to medical practitioners. *South African Medical Journal*, 1954, *28* : 48, p. 1024-1026

——— : La legge sugli stupefacenti all'esame della Camera (Examination of the narcotics law by the Chamber of Deputies). *Minerva Farmaceutica*, 1954, *3* : 10, p. 264-268

ARNOLD, W.; EBERT, L. : Neue Analysenmethoden zur Identifizierung von Arzneimitteln und Giftstoffen (New methods of analysis for identification of drugs and poisons). *Deutsche Zeitschrift für die gesamte gerichtliche Medizin*, 1954, *43* : 3, p. 252-258

B

BIANCHI, C.; FRANCESCHINI, J.: Experimental observations on Haffner's method for testing analgesic drugs. *British Journal of Pharmacology*, 1954, *9* : 3, p. 280-284

BOGS, U. : Zur Aschebestimmung der Drogen; ein Vorschlag für das DAB VII (Ash determination in drugs; proposal for the 7th editions of German Pharmacopeia). *Pharmazie* 1954, *9* : 11, p. 921-922

C

COOK, L.; NAVIS, G.; FELLOWS, E. J. : Enhancement of the action of certain analgetic drugs by β-diethylaminoethyldiphenylpropylacetate hydrochloride. *Journal of Pharmacology and Experimental Therapeutics*, 1954, *112* : 4, p. 473-479

COSSUTA, A. : Lo stato attuale delle analgesia e dell'anestesia ostetrica nelle cliniche Londinesi. I. (Current status of obstetrical analgesia and anesthesia in London clinics. I.). *Rivista d'Ostetricia e Ginecologia Pratica*, 1954, *36* : 10, p. 532-538

D

DADLEZ, J.; KAPCZYŃSKA, M.; WÓJCIAKOWA, Z. : Analiza barwna alkaloidów; jakościowa (Qualitative colorimetric analysis of alkaloids). *Farmacja Polska*, 1954, *10* : 8, p. 195-201

DAVIES, D. : Clinical testing of analgesics. *Acta Pharmacologica et Toxicologica*, 1954, *10* : 2, p. 113-116

DEGAN, P. : Razni aspekti problema kontrole lekova (Various aspects of the problems of drug control). *Arhiv za Farmaciju*, 1954, *4* : 5, p. 149-154

DONATELLI, L. : Il dolore ed i farmaci antidolorifici (Pain and pain-controlling drugs). *Rassegna internazionale di Clinica e Terapia*, 1954, *34* : 21, p. 695-698; *Ibid.*, 23, p. 773-776; *Ibid.*, 24, p. 800-802

E

EVANS, F. T. : The veins and the anaesthetist. *Journal of the Royal Institute of Public Health and Hygiene*, 1954, *17* : 11, p. 316-333

G

GUSEVA, E. N. : Deistvie boleutoliaiushchikh i nekotorykh drugikh veschestv pri eksperimental'nykh termicheskikh ozhogakh (Effect of analgesics and certain other substances on experimental thermal burns). *Biulleten' Eksperimental'noi Biologii i Meditsiny*, 1954, *38* : 10, p. 56-58

H

HOSEMANN, H. : Die schmerzarme Geburt (Painless delivery). *Medizinische Monatsschrift*, 1954, *8* : 9, p. 577-581

K

KROOK, G.; LINDGREN, G. : Kontrollen av handeln med narkotika i Sverige (Control of narcotics sales in Sweden). *Svensk Farmaceutisk Tidskrift*, 1954, *58* : 25, p. 591-597

KUSCHINSKY, G. : Wichtige Arzneimittel (Important drugs). *Deutsche Medizinische Wochenschrift*, 1954, *79* : 51, p. 1903-1904

L

LIUBLINA, E. I. : Vliianie nekotorykh farmakologicheskikh sredstv na dlitel'nost'narkoza, vyzvannogo raznymi narkotikami (Effect of certain pharmacologic media on duration of narcosis produced with various narcotics). *Farmakologiia I Toksikologiia*, 1954, *17* : 6, p. 6-12

LUPANT-ANDRÉ, F. : Caractérisation d'alcaloïdes par électrographie. *Annales de la Société Royale des Sciences Médicales et Naturelles de Bruxelles*, 1954, *7* : 3, p. 129-138

M

MACDONALD, A. D. : Le soulagement de la douleur. *Annales Pharmaceutiques Françaises*, 1954, *12* : 9-10, p. 663-671

MASSEBŒUF, A.; LEBASCLE; TEILHAUD : Remarques sur le choix de l'anesthésie en neurochirurgie. *Revue Neurologique*, 1954, *90* : 5, p. 621-625

MENDELSON, J.; GRENELL, R. G. : Effects of narcotics on coenzyme-A activity in acetylation. *Science*, 1954, 120 : 3124, p. 802-803

MERCIER, F.; MERCIER, J.; ETZENSPERGER, P.; ROUILLON, D. : Renforcement par les ganglioplégiques, des activités analgésique et anesthésique locale expérimentales. *Comptes Rendus des Séances de la Société de Biologie et de ses Filiales*, 1954, *148* : 15-18, p. 1448-1450

P

PLISNIER, H. : Etude comparative de l'action antitussigène des différents dérivés opiacés et synthétiques par rapport à celle du phosphate de codéine. *Thérapie*, 1954, *9* : 6, p. 737-751

PSCHYREMBEL, W. : Geburtserleichternde und schmerzlindernde Methoden (Methods of acceleration and analgetization in labour). *Deutsches Medizinisches Journal*, 1954, *5* : 19-20, p. 569-576; concl.

S

SALOHEIMO, A. : Suoneen annetavan nukutuksen Käytöstä pihtisynnytyksen yhteydessä (Intravenous anesthesia in forceps delivery). *Duodecim*, 1954, *70* : 7-8, p. 663-672

SÁNCHEZ HERNÁNDEZ, J. A. : Invernación artificial, analgesia y anestesia obstétricos (Artificial hibernation, analgesia and anesthesia in obstetrics). *Ginecología y Obstetricia de México*, 1954, *9* : 6, p. 422-434

SCHAUMANN, O.: Analgetika und protektives System (Analgesics and the protective system). *Deutsche Medizinische Wochenschrift*, 1954, 79-42, p. 1571-1573

SCHÖN, F. : Anestesia ed analgesia in stomatologia. *Rivista Italiana di Stomatologia*, 1954, *9* : 12, p. 1608-1620

STEVENSON, C. S. : Obstetric analgesia and anaesthesia; current problems. *Journal of the Michigan State Medical Society*, 1954, *53* : 8, p. 857-861

T

TRACKSDORF, H. : Abgrenzung, Phasen und Symptome des analgetischen Stadiums (Delimitation, phases and symptoms of the analgetic stage). *Zahnärztliche Rundschau*, 1954, *63* : 20, p. 590-593

V

VAILLE, C. ; STERN, G. : Les stupéfiants : fléau social; introduction. *Semaine Médicale Professionnelle et Médico-Sociale : Supplément à La Semaine des Hôpitaux*, 1954, *30* : 35, p. 857-860

VAILLE, C.; STERN, G. : Les stupéfiants : fléau social; historique. *Semaine Médicale Professionnelle et Médico-Sociale : Supplément à La Semaine des Hôpitaux*, 1954, *30* : 37, p. 925-932

VENHO, E. V.; VARTIAINEN, O.; VAPAAVUORI, M. : Vergleichende Versuche über die Wirkung verschiedener Atmungstimulanten. II (Comparative experimental studies on the effects of various respiratory stimulants). *Annales medicinae experimentalis et biologiae Fenniae*, 1954, *32* : 2, p. 203-213

VOLKE, J.; VOLKEOVÁ, V. : Polarografické chování alkaloidù (Polarographic behaviour of alkaloids). *Ceskoslovenska Farmacie*, 1954, *3* : 8, p. 289-292

W

WALLER, H. S. : The legal effect of the 1954 amendment to the Federal Narcotic law (the so-called Codeine Act). *South Dakota Journal of Medicine and Pharmacy*, 1954, *7* : 11, p. 419-420

Z

ZINNITZ, F.; KOLWEL, E. : Die analgetische Wirkung im Elektrodermatogramm (Analgetic effects in the electrodermatogram). *Medizinische Monatsschrift*, 1954, *8* : 6, p. 385-388

Part II. OPIUM POPPY, OPIUM AND DRUGS MANUFACTURED THEREFROM

A. Opium poppy, opium and opium alkaloids collectively considered

C

CHENG, Shu Sing : A double-coloration test for the differentiation of opium alkaloids. *Journal of the American Pharmaceutical Association : Scientific Edition*, 1954, *43* : 12, p. 767-769

CLARKE, W. A.; McBAY, A. J. : Spectrophotometric determination of morphine and codeine. *Journal of the American Pharmaceutical Association*, 1954, *43*, p. 39

D

DAURI, A.; GALLOZZI, E. : Il comportamento del metabolismo basale dopo medicazione preanastetica con l'oppio e con i suoi derivati (Behaviour of basal metabolism after pre-anaesthetic administration of opium and its derivatives). *Annali italiani di chirurgia*, 1954, *31* : 7, p. 578-587

L

LA BARRE, J.; PLISNIER, H. : Etude comparative sur les actions antitussigène et toxique de la codéine, de la dihydrocodéinone, de l'acétyldéméthyldihydrothébaïne par rapport à celles de la diacétylmorphine (héroïne). *Bulletin de l'Académie Royale de Médecine de Belgique*, 1954, *19* : 10, p. 445-460

S

SCHNEIDER, E. : Postoperative Analgesie mittels Medikamentkombination (Postoperative analgesia with drug combination). *Praxis*, 1954, *43* : 43, p. 922-923

V

VAILLE, C.; STERN, G. : Les stupéfiants : fléau social; l'opium. *Semaine Médicale Professionnelle et Médico-Sociale; Supplément à La Semaine des Hôpitaux*, 1954, *30* : 39, p. 997-1007

VAILLE, C.; STERN, G. : Limitation de la production et de l'emploi de l'opium. *Annales pharmaceutiques françaises*, 1954, *12* : 6, p. 61-67; 1954, *12* : 7-8, p. 77-89

B. Morphine, Apomorphine

A

AFANAS'EVA, E. A. : K farmakologii morfina (Pharmacology of morphine) *Farmakologiia I Toksikologiia*, 1954, *17* : 5, p. 23-26

ANDREW, R. : Gastric and intestinal motility studies with morphine, atropine, hexamethonium bromide and " banthine ". *Australasian Annals of Medicine*, 1954, *3* : 4, p. 305-311

B

BÖLCS, B. : Sertürner Frigyes Vilmos; a morfin felvedezése (Frederick Wilhelm Sertürner, the discoverer of morphine). *Gyógyszerész*, 1954, *9* : 12, p. 221-223

BUCHEGGER, G.; FRISCH, P. : Zur Vervollständigung der absoluten Bettruhe bei der Behandlung der cavernösen Lungentuberkulose (Completion of absolute bed rest in the treatment of cavitary pulmonary tuberculosis). *Medizinische Klinik*, 1954, *49* : 46, p. 1846-1849

BUCHSBAUM, R.; KUNTZ, J. A. : The effects of certain stimulants and depressants on individual fibroblasts in a perfusion chamber. *Annals of the New York Academy of Sciences*, 1954, *58* : 7, p. 1303-1310

D

DEBRAY, C.; JOURDE, L.; LE CANUET, R. : Utilisation de la morphine dans la cholangiographie par voie veineuse. *Archives des Maladies de l'Appareil Digestif et des Maladies de la Nutrition*, 1954, *13* : 11, p. 1086-1095

E

ENGELMEIER, M. P. : Ein Selbsttötungsversuch mit E 605 und seine Behandlung mit einem Allylderivat aus der Gruppe der Morphinane (A suicide attempt with E 605 and its treatment with allylnormorphine). *Medizinische Klinik*, 1954, *49* : 50, p. 1996-1997

F

FOGHT-NIELSEN, V. : Morfinforgiftning behandlet med N-allyl-nor-morfin (Nalorphine therapy of morphine poisoning). *Ugeskrift for Laeger*, 1954, *115* : 37, p. 1327-1328

G

* GOTTSEGEN, G.; ROMODA, T.; BARTÓK : The effect of morphine on respiration and oxygen consumption in heart disease. *Acta Medica Academiae Scientiarum Hungaricae*, 1954, *6* : 3-4, p. 355-366

GROSS, F.; KAUFMANN, H. : Hemmung der analgetischen Wirkung von Morphin und Cliradon durch verschiedene Zucker und Zuckerabbauprodukte (Inhibition of analgesic effect of morphine and cliradon by various sugars and intermediary products of sugars). *Helvetica Physiologica et Pharmacologica Acta*, 1954, *12* : 4, p. 284-292

GRÜNER, O. : Über den qualitativen und quantitativen Morphinnachweis mittels Deckertscher Probe (Qualitative and quantitative morphine determination in Decker's test). *Deutsche Zeitschrift für die Gesamte Gerichtliche Medizin*, 1954, *43* : 3, p. 259-262

K

KEMPE, H. D. : Untersuchungen zur Frage der strukturchemischen Verwandtschaft von Morphin und Papaverin mit Hilfe des Nalorphin-Antagonismus (Nalorphine antagonism as an aid in the study of structural relationship of morphine and papaverine). *Naunyn-Schmiedebergs Archiv Für Experimentelle Pathologie und Pharmakologie*, 1954, *223* : 6, p. 541-553

L

LONGO, V. G.; NAPOLITANO, L. : Farmacologia del riflesso vertibolo-oculare. III. Azione dell'ortotoluolossipropandiolo (mephenesin), della morfina, della eserina e del DFP sul nistagmo postrotatorio nel coniglio dopo asportazione del telencefalo (Pharmacology of the vestibulo-ocular reflex. III. Action of 3-o-tolyloxy-1, 2-propanediol (mephenesin), of eserine, and of DFP on post-rotatory nystagmus in rabbits after removal of the telencephalon). *Archives Internationales de Pharmacodynamie et de Thérapie*, 1954, *99* : 2, p. 215-223

M

MANNELLI, A.; VILLEVIELLE, L.; ZARA, A. : Il dilaudid in preanestesia. *Giornale Italiano di Chirurgia*, 1954, *10* : 10, p. 836-848

MILLER, J. W.; ANDERSON, H. H. : The effect of N-demethylation on certain pharmacologic actions of morphine, codeine, and meperidine in the mouse. *Journal of Pharmacology and Experimental Therapeutics*, 1954, *112* : 2, p. 191-196

MILOSEVIĆ, M. P. : Dejstvo morfina, petidina i metadona na peristaltičku aktivnost creva (Effect of morphine, pethidine and methadone on peristaltic activity). *Acta Medica Yugoslavica*, 1954, *8* : 2, p. 189-195

MORACCI, E. : Esta justificado el uso de la morfina en la terapeutica medica de la eclampsia? (Is the use of morphine justified in medical therapy of eclampsia?). *Obstetricia y Ginecologia Latino-Americanas*, 1954, *12* : 11-12, p. 539-546

N

NADAL, R.; JOURDE, L. : Cholangiographie par voie veineuse et morphine. *Journal de Radiologie et d'Electrologie et Archives d'électricité médicale*, 1954, *35* : 9-10, p. 776-777

O

OLEJARCZUKOWA, G. : Wpływ morfiny na pobudliwość układu przedsion Kowego u Królika (Effect of morphine on vestibular irritability in rabbit). *Acta physiologica Polonica*, 1954, *5* : 3, p. 334

ORAHOVATS, P. D.; WINTER, C. A.; LEHMAN, E. G. : Pharmacological studies of mixtures of narcotics and N-allylnormorphine. *Journal of Pharmacology and Experimental Therapeutics*, 1954, *112* : 2, p. 246-251

P

PELLICCIONI, F. : Sull'azione ipnotica dell'apomorfina (Hypnotic effect of apomorfina). *Atti dell'Academia dei Fisiocritici in Siena; Sezione Medico-Fisica*, 1954, Vol. 1, p. 188-195

POGÁDY, J.; JANÍK, A.; ZEMAN, L.; ZIKMUND, V. : Prispevok k liečbe alkholizmu apomorfinom (Contribution to the therapy of alcoholism with apomorphine). *Lekársky Obzor*, 1954, *3* : 5, p. 278-281

POULSEN, T. : Experimental investigations into the effects of morphine and aprobarbital on carbon-dioxide provoked pulmonary œdema in mice. *Acta Pharmacologica et Toxicologica*, 1954, *10* : 3, p. 246-252

R

RATTENBORG, C.; SONNE, L. M. : Kontinnerlig ventilations og respirations registrering belyst ved et tilfaelde af Ketoganforgiftning, behandlet medanarcon (Continuous ventilation and respiration recording demonstrated in a case of Ketogan poisoning treated with nalorphine). *Ugeskrift for Laeger*, 1954, *116*: 45, p. 1605-1607

S

SCHNEIDER, J. A. : Reserpine antagonism of morphine analgesia in mice. *Proceedings of the Society for Experimental Biology and Medicine*, 1954, *87* : 3, p. 614-615

SCREMIN, L.; TADDEI, I. : Osservazioni farmacologiche ed esperienze scolastiche (Pharmacologic observations and scholastic experiments). *Atti dell'Academia dei Fisiocritici in Siena; Sezione Medico-Fisica*, 1954, Vol. 1, p. 161-171

SONNE, L. M. : Antagoniststoffer mod morfinpraeparater (Compounds antagonistic to morphine preparations). *Ugeskrift for Laeger*, 1954, *116* : 37, p. 1312-1315

SONNE, L. M. : Ketogan forgiftning behandlet med anarcon (Nalorphin therapy of Ketogan poisoning). *Ugeskrift for Laeger*, 1954, *116* : 45, p. 1607-1608

SUPRUN, P. P. : Kolichestvennoe opredelenie morfina v nastoike opiia (Quantitative determination of morphine in opium tincture). *Aptechnoe Delo*, 1954, *3* : 6, p. 45-46

* SZABOLCS, L. : (Colorimetric method for quantitative determination of morphine). *Hungarian Journal of Chemistry*, 1953, *59*, p. 67

T

TABUSSE, L. : Morphine et anoxémie. *Médecine Aéronautique*, 1954, *9* : 3, p. 301-304

TANIEWSKI, J. : O nadużywaniu morfiny w otolaryngologii (Abuse of morphine in otolaryngology). *Otolaryngologia Polska*, 1954, *8* : 3, p. 215-218

TEIXEIRA, J. P. : Efeitos da morfina no meu próprio caso (Effects of morphine in my own personal case). *Revista Brasileira de Medicina*, 1954, *11* : 8, p. 566-569

V

VAN DER STRAETEN, M; VERBEKE, R.; VERMEULEN, A.: Acidose respiratoire provoquée par l'inhalation d'oxygène ou l'administration de morphine. *Acta Clinica Belgica*, 1954, *9* : 5, p. 383-400

W

WIKLER, A. : Clinical and electroencephalographic studies on the effects of mescaline, N-allylnormorphine and morphine in man; a pharmacologic analysis of the functions of the spontaneous electrical activity of the cerebral cortex. *Journal of Nervous and Mental Disease*, 1954, *120* : 3-4, p. 157-175

WILSON, A. : Current therapeutics. LXXXIV. Nalorphine. *Practitioner*, 1954, *173* : 1038, p. 717-722

C. Other phenanthrene alkaloids and derivatives of opium

A

ALFONSI, P. L.; PACI, G. : Il controllo del dolore postoperatorio mediante una nuova associazione analgesica; osservazioni cliniche (Control of postoperative pain with a new analgesic compound; clinical study). *Minerva Chirurgica*, 1954, *9* : 20, p. 943-944

G

GONDIM, J. C. : A associação cloridrato de di- hidro- oxi -codeinoma, bromidrato de escopolamina e efetonina, como analgésico nas cretagens uterinas post-abortum (Combined chlorhydrate of dihydroxycodeinone, scopolamine hydrobromide and ephetonin as analgesic in postabortion uterine curettage). *Revista de Gynecologia e d'Obstetricia*, 1954, *48* : 6, p. 750-753

M

MILLER, J. W.; ANDERSON, H. H. : The effect of N-demethylation on certain pharmacologic actions of morphine, codeine, and meperidine in the mouse. *Journal of Pharmacology and Experimental Therapeutics*, 1954, *112* : 2, p. 191-196

P

PERNAROWSKI, M.; CHATTEN, L. G.; LEVI, L. : The determination of codeine phosphate in combination with acetylsalicylic acid, phenacetin, and caffeine by nonaqueous titration. *Journal of the American Pharmaceutical Association; Scientific Edition*, 1954, *43* : 12, p. 746-750

PIPER, C. E.; NICKLAS, F. W. : Percodan for pain in industrial practice. *Industrial Medicine and Surgery*, 1954, *23* : 11, p. 510-512

W

WIBERG, G. S.; TUBA, J. : The effect of codeine on rat serum amylase. *Canadian Journal of Biochemistry and Physiology*, 1954, *32* : 6, p. 625-627

D. Other drugs and substances derived from the opium poppy

B

BATTEZZATI, M.; TAGLIAFERRO, A. : Sulla patogenesi delle arteriopatie obliteranti croniche periferiche. II. Ricerche sperimentali sul circolo degli arti sotto azione della papaverina (Pathogenesis of chronic peripheral obliterating arteriopathy. II. Experimental study of the effect of papaverine on the circulation of the extremities). *Minerva Chirurgica*, 1954, *9* : 22, p. 1072-1074

K

KEMPE, H. D. : Untersuchungen zur Frage der Strukturchemischen Verwandtschaft von Morphin und Papaverin mit Hilfe des Nalorphin-Antagonismus (Nalorphine antagonism as an aid in the study of structural relationship of morphine and papaverine). *Naunyn-Schmiedebergs Archiv Für Experimentelle Pathologie und Pharmakologie*, 1954, *223* : 6, p. 541-553

KONZETT, H.; ROTHLIN, E.: Zur Wirkung von Narkotin auf den Hustenreflex und auf die Bronchialmuskulatur (The effect of narcotine on cough reflex and on bronchial musculature). *Experientia*, 1954, *10* : 11, p. 472-473

M

MIRONENKO, A. I. : Vliianie papverina na sosudy izolirovannogo ukha krolika pri sokhranennoi nervnoi sviazi egos tsentral'noi nervnoi sistemoi (Effect of papaverine on blood vessels of isolated rabbit ear with preservation of neural connection with the central nervous system). *Farmakologiia i Toksikologiia*, 1954, *17* : 5, p. 33-36

P

PYKHTINA, A. A. : Kanalizu deistviia papaverina (Analysis of the effect of papaverine). *Farmakologiia i Toksikologiia*, 1954, *17* : 6, p. 33-36

Part III. THE COCA LEAF AND COCAINE

C

CRAPANZANO, H. E. : La coca en el altiplano; interpretación fisiológica de su acción (Coca in the highlands; physiological interpretation of its effects). *Día Médico*, 1954, *26* : 83, p. 2464-2467

Q

QUEVAUVILLER, A.; BLANPIN, O. : L'activité anesthésique locale de surface du chlorhydrate de cocaïne est inhibée par certains mouillants non ioniques (tweens). *Annales Pharmaceutiques Françaises*, 1954, *12* : 9-10, p. 646-649

QUIVY, D. : Sur l'amplification par la cocaïne, des effets hypertenseurs de l'adrénaline. *Journal de Physiologie*, 1954, *46* : 4, p. 861-866

R

RAYMOND-HAMET : Influence de la cocaïnisation sur l'action hypertensive et vasoconstrictive rénale de la bufoténidine. *Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences*, 1954, *239* : 25, p. 1881-1883

V

VAILLE, C.; STERN, G. : Les stupéfiants : Fléau social; la coca. *Semaine Médicale Professionnelle et Médico-Sociale : Supplément à La Semaine des Hôpitaux*, 1954, *30* : 44, p. 1169-1174

Part IV. CANNABIS AND ITS DERIVATIVES

D

DUQUÉNOIS, P. : Essai d'identification du hachisch et du chanvre à l'aide de la microchromatographie. *Annales de médecine légale et de criminologie*, 1954, *34* : 5, p. 224-225

R

ROLLS, E. J.; STAFFORD-CLARK, D. : Depersonalization treated by cannabis indica and psychotherapy. *Guy's Hospital Reports*, 1954, *103* : 4, p. 330-336

V

VAILLE, C.; STERN, G. : Le Cannabis. *Semaine Médicale Professionnelle et Médico-Sociale; Supplément à la Semaine des Hôpitaux*, 1954, *30* : 42, p. 1105-1111

Part V. SYNTHETIC DRUGS

A. General Works

A

ANONYMOUS : Nuovi farmaci e nuovi apparecchi elettro-medicali alla Mostra Medica Londinese (New drugs and new electromedical apparatus at the London Medical Exposition). *Minerva Medica*, 1954, *45* : 102, p. 1030-1031

AREZIO, G.; PERUZZO, L.; VERGA, G. : Azione del cocktail vegetativolitico sul surrene di ratto sottoposto a stress (Effect of vegetativolytic cocktails on the adrenal glands of rats subjected to stress). *Acta Anaesthesiologica*, 1954, *5* : 3, p. 137-151

B

BECKETT, A. H.; CASY, A. F. : Synthetic analgesics : stereochemical considerations. *Journal of Pharmacy and Pharmacology*, 1954, *6* : 12, p. 986-1001

M

MUEHLAU, M. : Ist die Forderung berechtigt, die neuen stark wirkenden synthetischen Analgetica insb. Polamidon, Cliradon, Dromoran, dem Opiumgesetz zu unterstellen (Is it justified to place the new synthetic analgesics such as Polamidon, Cliradon and Dromoran under the opium law?). *Aerstliche Wochenschrift*, 1952, p. 257-260

S

SCHAUMANN, O. : Die Wirkungsspezifität der morphinähnlichen Analgetica (Specific action of morphine-like analgesics). *Arzneimittel-Forschung*, 1954, *4* : 1, p. 115-116

B. Pethidine and related compounds

D

DUTTA, N. K.; TAMHANE, R. G. : Effect of atropine, pethidine, procaine, quinidine and prophen pyridamine maleate on the histamine-induced gastric acidity in cats. *Indian Journal of Medical Research*, 1953, *41* : 1, p. 45-50

E

EIDINOVA, M. B. : Primenenie promedola pri zabolevaniakh nervnoi sistemy (Use of promedol in diseases of the nervous system). *Sovetskaia Meditsina*, 1954, *18* : 11, p. 12-14

F

FRANKS, E. H. : Anaesthesia for intra-nasal and intra-oral operations in adults; trial of a technique based on intravenous pethidine. *British Journal of Anaesthesia*, 1954, *26* : 6, p. 418-426

G

GERCHOW, J. : Über eine primäre Cliradonsucht (Primary cliradon addiction). *Deutsche Zeitschrift für die gesamte gerichtliche Medizin*, 1954, *43* : 3, p. 242-244

GROSS, F.; KAUFMANN, H. : Hemmung der analgetischen Wirkung von Morphin und Cliradon durch verschiedene Zucker und Zuckerabbauprodukte (Inhibition of analgesic effect of morphine and cliradon by various sugars and intermediary products of sugars). *Helvetica Physiologica et Pharmacologica Acta*, 1954, *12* : 4, p. 284-292

K

KOPERA, J.; ARMITAGE, A. K. : Comparison of some pharmacological properties of chlorpromazine, promethazine, and pethidine.

British Journal of Pharmacology and Chemotherapy, 1954, *9* : 4, p. 392-401

L

LASAGNA, L.; BEECHER, H. K. : The analgesic effectiveness of codeine and meperidine (demerol). *Journal of Pharmacology and Experimental Therapeutics*, 1954, *112* : 3, p. 306-311

M

MILLER, J. W.; ANDERSON, H. H. : The effect of N-demethylation on certain pharmacologic actions of morphine, codeine, and meperidine in the mouse. *Journal of Pharmacology and Experimental Therapeutics*, 1954, *112* : 2, p. 191-196

MILOSEVIĆ, M. P. : Dejstvo morfina, petidina i metadona na peristaltičku aktivnost creva (Effect of morphine, pethidine and methadone on peristaltic activity). *Acta medica Iugoslavica*, 1954, *8* : 2, p. 189-195

R

ROST, H.; SIEVERT, C. : Die Einwirkung von Phenothiazinderivaten und Dolantin auf Diurese und Nierenclearance (Effects of phenothiazine derivatives and dolantin on diuresis and kidney clearance). *Zentralblatt Für Gynäkologie*, 1954, *76* : 49, p. 2148-2153

S

SIKER, E. S.; FOLDES, F. F.; PAHK, N. M.; SWERDLOW, M. : Nisentil (1, 3, dimethyl-4-phenyl-4-propionoxy piperidine) : a new supplement for nitrous oxide oxygen, thiopentone (pentothal sodium) anaesthesia. *British Journal of Anaesthesia*, 1954, *26* : 6, p. 405-410

W

WILSON, D. R. : A simplified closed system, using only intravenous anaesthesia with relaxants, and a preliminary report on dosage results. *Medical Journal of Australia*, 1954, *2* : 17, p. 659-662

C. Methadone and related compounds

A

ANOSOV, N. N.; PISAREVA, N. A : Lechenie fenadonom bol'nyk s nevralgicheskim sindromom razlichnogo proiskhozhdeniia (Therapy of neuralgic syndromes of various origins with phenadon). *Sovetskaia Meditsina*, 1954, *18* : 11, p. 11-12

B

BERÍC, B. : Bezbolni porodjaji polamidonom S. (Painless labour with polamidone S.). *Medicinski Glasnik*, 1954, *8* : 9, p. 316-317

BURKHARDT, H.; ORZECHOWSKI, G. : Ticardasucht (Ticarda addiction). *Archiv Für Toxikologie; Führer-Wielands Sammlung von Vergiftungsfällen*, 1954, *15* : 2, p. 135-140

M

MILOSEVIĆ, M. P. : Dejstvo morfina, petidina i metadona na peristaltičku aktivnost creva (Effect of morphine, pethidine and methadone on peristaltic activity). *Acta medica Iugoslavica*, 1954, *8* : 2, p. 189-195

N

NAEVE, W.; KÖRNER, K. F. : Tod durch Polamidonüberdosierung bei einem Kleinkinde (Overdose of methadon causing death in infant). *Archiv Für Toxikologie; Führer-Wielands Sammlung von Vergiftungsfällen*, 1954, *15* : 2, p. 96-99

P

PELLMONT, B.; BAECHTOLD, H. : Pharmakologie der Romilar Roche, einer hustenhemmenden Substanz mit zentralem Angriffis punkt (Pharmacology of Romilar Roche, a cough-inhibiting substance with attack of the central point). *Schweizerische Medizinische Wochenschrift*, 1954, *84* : 49, p. 1369-1372

PERSCH, R. : Über Polamidon-Missbrauch (Misuse of polamidon). *Psychiatrie, Neurologie und Medizinische Psychologie*, 1954, *6* : 10, p. 258-263

S

SANDER, M. : Basische 1, 1-Diphenylalkanderivate, ihr Chemismus und ihre Bedeutung als Analgetica (Polamidon). I. (Basic 1, 1-Diphenylalkyl derivatives, chemistry and value as analgesics (polamidon)). *Arzneimittel-Forschung*, 1954, *4* : 3, p. 183-189, *ibid.* *4* : 4, p. 257-262

STÖRMER, A. : Das Schocksyndrom beim akuten Myokardinfarkt und seine Behandlung (The shock syndrome in acute myocardial infarction and its treatment). *Münchener Medizinische Wochenschrift*, 1954, *96* : 36, p. 1011-1014

D. Morphinan and morphine synthesis

A

AKÇASU, A. : Yeni bir analjezik drog metorphinane (dromoran Roche) (A new analgesic, 3-hydroxy-N-methylmorphinan). *Tip Fakültesi Mecmuasi*, 1954, *17* : 4, p. 530-536

C

CAVACIUTI, P.; ROLANDI, L. : Un nuovo analgesico di sintesi : l'idrossi-N-metil morfinano in anestesia (A new synthetic analgesic; hydroxy-N-methyl morphine in anesthaesia). *Ospedale Maggiore*, 1954, *42* : 8, p. 374-379

D

DAURI, A.; GALLOZZI, E. : Il tartrato del 3-idrossi-N-metil-morfinano quale analgesico di mantenimento in anestesia generale (Tartrate of 3-hydroxy-N-methyl-morphinan as analgesic maintaining general anesthesia). *Acta Anaesthesiologica*, 1954, *5* : 1, p. 1-14

E

ECKENHOFF, J. E.; FUNDERBURG, L. W. : Observations on the use of the opiate antagonists nalorphine and levallorphan. *American Journal of Medical Sciences*, 1954, *228* : 5, p. 546-553

H

HOTTINGER, A. : Klinische Erfahrungen mit Romilar einem neuen synthesischen Hustenmittel (Clinical experience with Romilar, a new synthetic cough medicine). *Schweizerische Medizinische Wochenschrift*, 1954, *84* : 49, p. 1372-1374

P

PEUKERT, E. : Klinische Erfahrungen mit Citarin, einem neuen stark wirkenden Analgetikum (Clinical experience with citarin, a neu effective analgesic). *Die Medizinische*, 1954, No. 37, p. 1251-1252

V

VITOLO, A. E.; VENTURA, R. : Ricerche chimiche e microchimiche per la caratterizzazione del (-)-3-ossi-N-metilmorfinano e del dl-6-dimetilamino-4 : 4-difenileptanone-3- (Chemical and microchemical studies on characteristics of (-)-3-hydroxy-N-methylmorphine and of 6-dimethylamino-4, -4-diphenyl-3-heptanone). *Bolletino della Societa Italiana di Biologia Sperimentale*, 1954, *30* : 6, p. 668

Part VI. ADDICTION TO NARCOTIC DRUGS

B

BELL, R. G. : Dependence upon depressant chemicals. *Canadian Nurse*, 1954, *50* : 10, p. 800-802

BONEBAKKER, A. : De behandeling van opiumschuivers en morphinisten (Treatment of opium lurchers and morphinists). *Nederlands Tijdschrift Voor Geneeskunde*, 1954, *98*: 45, p. 3230-3240

BÜHLER, F. : Ticarda-Süchtigkeit (Ticarda addiction). *Medizinische*, 1954, No. *37*, p. 1245-1246

D

DORDONI, F.; PICCINELLI, D. : Sulla assuefazione ai farmaci irritanti (Development of tolerance to irritants). *Archivio Italiano di Scienze Farmacologiche*, 1954, *4* : 3, p. 285-287

F

FOLDES, F. F.; SWERDLOW, M. : The use and abuse of anaesthetic drugs. *Pennsylvania Medical Journal*, 1954, *57* : 12, p. 1160-1167

FOX, J. de W. : Narcotic addiction among physicians. *Medical Arts and Sciences*, 1954, *8* : 4, p. 96-100

FRIEDMAN, E. : Multipolar electrocoma therapy. V. The use of three lead, prolonged electrocoma (PEC-3) in cases of severe phobic-anxiety and addictions. *Confina Neurologica*, 1954, *14* : 5, p. 264-268

G

GOULD, I. B.; SMITH, L.; BARKER, W.; GAMSO, R. R. : A specific approach to the vocational needs of adolescent users of narcotics at Riverside Hospital. *Psychiatric Quarterly Supplement*, 1954, *28* : 2, p. 199-208

K

KALDEGG, A. : Three drug addicts; test results and implications. *Guy's Hospital Reports*, 1954, *103* : 4, p. 348-359

KORNETSKY, C. : Relationship between Rorschach determinants and psychosis in barbiturate withdrawal syndrome. *A. M.A. Archives of neurology and psychiatry*, 1954, *72* : 4, p. 452-454

M

MEERLOO, J. A. : Abstention, rebound, and readjustment; addiction abstention, acute deprivation, starvation, shock, withdrawal of chronic medication : a study in experimental adaptation. *Journal of Nervous and Mental Disease*, 1954, *120* : 1-2, p. 46-55

MERCIER, J.; SESTIER, M. R. : Détermination de l'accoutumance à la morphine et de l'influence du sevrage en toxique par une méthode psycho-physiologique. *Annales Pharmaceutiques Françaises*, 1954, *12* : 6, p. 458-465

P

PATERSON, A. S. : Addiction to morphia and allied drugs; some recent developments. *Postgraduate Medical Journal*, 1954, *30* : 350, p. 622-625

S

SLOCUM, H. C. : Problems of overtreatment of surgical patients with depressant drugs. *Journal of the American Medical Association*, 1954, *156* : 17, p. 1573-1575

W

WILLIAMS, E. Y. : The problem of drug addiction. *Journal of the National Medical Association*, 1954, *46* : 6, p. 398-400

ERRATUM

In Volume VII, No. 2, of the *Bulletin*,

on *page 28* the first sentence, second line, instead of " 1954 " read " *1955* ";

on *page 29*, the first sentence of article " Twentieth Session of the Economic and Social Council ", after " At its twentieth session " insert the words : " held in Geneva from 5 July to 5 August 1955,";

on *page 30*, the heading should read :

" Expert Committee of the World Health Organization on Drugs Liable to Produce Addiction ";

on *page 32*, line 8, instead of " Department of Social Affairs " read " Department of Economic and Social Affairs ".